NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Premeeting briefing

Contains AIC ,CIC

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the committee meeting

COMMON ABBREVIATIONS	
PD-1	programmed death
IC	investigator choice
BSC	best supportive care
CS	company submission
ERG	evidence review group
ITT	intention to treat
SCCHN	squamous-cell carcinoma of the head and neck
R/M	recurrent or metastatic
HRQoL	health related quality of life
SLR	systematic literature review
BOR	Best overall response
CR	complete response
PR	partial response
PFS	progression-free survival
OS	overall survival
DOR	duration of response
TTD	time to treatment duration
PRO	patient reported outcomes
ICER	incremental cost-effectiveness ratio
QALY	quality-adjusted life year

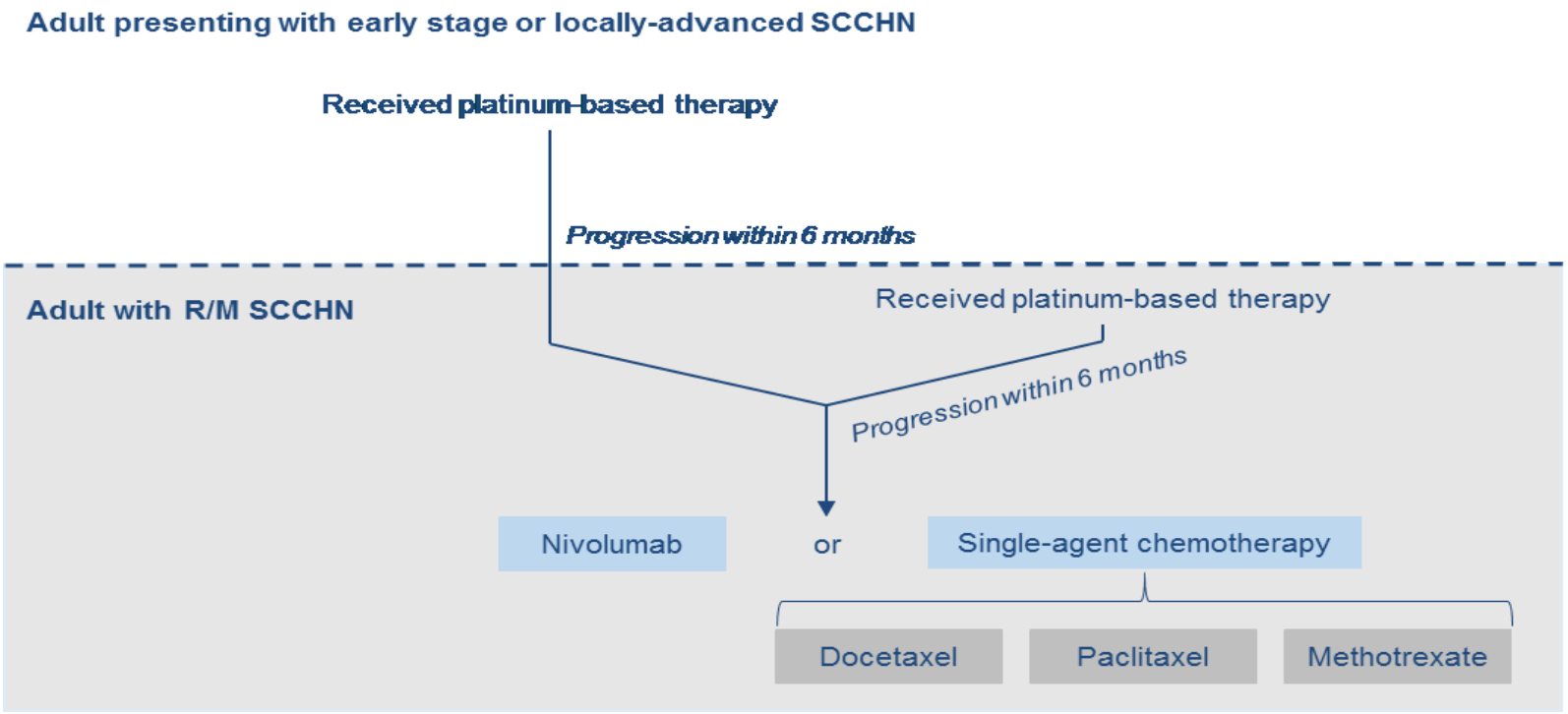
Disease background & management

- Head and neck cancers include tumours arising mainly in the oral cavity, pharynx and larynx
- Excludes tumours of the brain and related tissues
- >90% of malignant tumours in the head and neck are squamous cell carcinomas
- Approximately 60% of patients with squamous cell carcinoma of the head and neck (SCCHN) present with advanced stage disease
  - 20–30% of them go on to develop recurrent or metastatic (R/M) disease.
- 4% of patients in the UK will present with metastatic disease
- Platinum-based therapies predominantly used for SCCHN
- Variation in clinical practice after platinum therapy, but may include docetaxel, paclitaxel, methotrexate, cetuximab
- No NICE guidance for SCCHN after platinum therapy

Details of technology

Technology	Nivolumab (Opdivo, Bristol-Myers Squibb)
Anticipated Marketing authorisation	Nivolumab is indicated for the treatment of recurrent or metastatic squamous-cell cancer of the head and neck after platinum-based therapy in adults.”
Mechanism of action	Acts as an immune-checkpoint inhibitor that targets the programmed death (PD-1) inhibitor by preventing inactivation of T-cells and restoring T-cell activity against tumour cells by harnessing the patient’s own immune system to directly fight cancer cells.
Administration	Intravenous infusion, over 60-minutes 3 mg/kg every 2 weeks
Acquisition cost	List price: £439.00 (40 mg vial) and £1,097.00 (100 mg vial) PAS price: *****(40 mg vial) and ***** (100 mg vial)
Cost of a course of treatment	Based on results of the economic analysis, the average cost of nivolumab is estimated to be: List price: ****** PAS price: ******

Clinical care pathway for adults with R/M SCCHN who have progressed after platinum-based therapy



- Patients who may be considered eligible for treatment with nivolumab under the anticipated indication for SCCHN are expected to have progressed within 6 months of having received platinum-based therapy, but may have received this therapy in either early or locally advanced disease setting.
- Docetaxel is the most routinely-used agent in UK clinical practice for patients with R/M SCCHN who have progressed after platinum-based therapy.

Patients perspective

- Patient health related quality of life (HRQoL) has been shown to be associated with disease stage. Patients with late-stage SCCHN have worse HRQoL compared to those with earlier-stage disease.
- Once R/M SCCHN patients have progressed on previous platinum based chemotherapy, the prognosis is poor. No standard second or third line therapy although taxane based chemotherapy used and great variation between different centres.
- Some variation in the choice of second line chemotherapy e.g paclitaxel or docetaxel and either single agent or in combination another with platinum based chemotherapy such as carboplatin.
- As cytotoxic chemotherapy is the most routinely-used treatment approach, platinum-refractory R/M SCCHN patients may experience further deterioration in HRQoL due to drug-related adverse events (AEs) in addition to the impact of worsening disease symptoms.
- Unmet medical need for effective treatments that can maintain levels of HRQoL for R/M patients who are refractory to platinum-based therapy. All active therapy options associated with significant toxicity and relatively low response rates

Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission
Population	Adults with R/M SCCHN who have previously received platinum-based chemotherapy.	Adults with R/M SCCHN who have previously received platinum-based chemotherapy.
Intervention	Nivolumab	Nivolumab
Comparator(s)	• Docetaxel • Paclitaxel • Methotrexate	• Docetaxel • Paclitaxel • Methotrexate
Outcomes	• Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life

Note: there were no direct or indirect comparisons made with nivolumab and paclitaxel due to insufficient data. Equivalency in OS was assumed for all comparators in scope

Clinical effectiveness evidence

company submission chapter 4

Clinical evidence

Clinical evidence supporting the use of nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after receiving platinum-based therapy presented from a single phase III RCT CheckMate 141

Trial name	CheckMate 141
Population	Adult patients with platinum-refractory R/M SCCHN
Intervention	Nivolumab group (n=240) 3 mg/kg, i.v. infusion, Q2W
Comparator(s)	Patients randomised received one of the three possible therapies at the discretion of the investigator (Investigator's choice n=121): • Docetaxel (30 mg/m2, i.v. infusion, QW) (n=54, 47%) • Methotrexate (40 mg/m2, i.v. infusion, QW) (n=52, 41%) • Cetuximab (400 mg/m2, i.v. infusion, once, then 250 mg/m2, i.v., QW) (n=15, 12%)
Location	55 international study sites across 15 countries in North America, South America, Europe and Asia. 34 UK patients randomised to study treatment at 5 study sites.
Trial design	Multicentre, open-label, phase III randomised controlled trial
Method of randomisation	Patients were randomised (2:1) to receive either nivolumab or IC of therapy, with stratification by prior cetuximab treatment (yes or no).
Eligibility criteria for participants	**Key inclusion criteria**: • Males and females ≥18 years of age • Histologically confirmed R/M SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) • Tumour progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant, primary, recurrent, or metastatic setting

CheckMate 141 contd.

	CheckMate 141
Baseline characteristics	Higher proportion of former/current smokers in the nivolumab arm (79.6%) compared to the IC arm (70.2%). Majority of patients in the nivolumab (****) and IC arms (******)had received prior cetuximab (yes/no) (the only stratification factor at randomisation) Subsequent anti-cancer therapy was received by ****** and *******of patients in the nivolumab and IC arms, respectively Overall, patient characteristics were well balanced in the two study arms. Patients randomised to study treatment in CheckMate 141 were typically male (83.1%), white (83.1%) ,former/current smokers (76.5%) and the median age was 60 years. The company stated that this is generally consistent with the patient population expected to present with SCCHN in UK clinical practice.
Subgroups	A pre-planned exploratory subgroup analysis of OS by treatment group and PD-L1 expression (≥1% or <1%) was conducted. The following exploratory analyses were also added after database lock to help further characterise the study results: •OS of nivolumab versus IC by HPV-p16 status (positive or negative) •OS of nivolumab versus IC by selected demographic and baseline characteristics, including intended therapy for the IC arm
Duration of study and follow-up	At data cut-off point, median duration of follow-up was 5.3 months (range, 0.0–16.8) in the nivolumab arm and 4.6 months (range, 0.0–15.2) in the IC arm

Outcomes of the trial

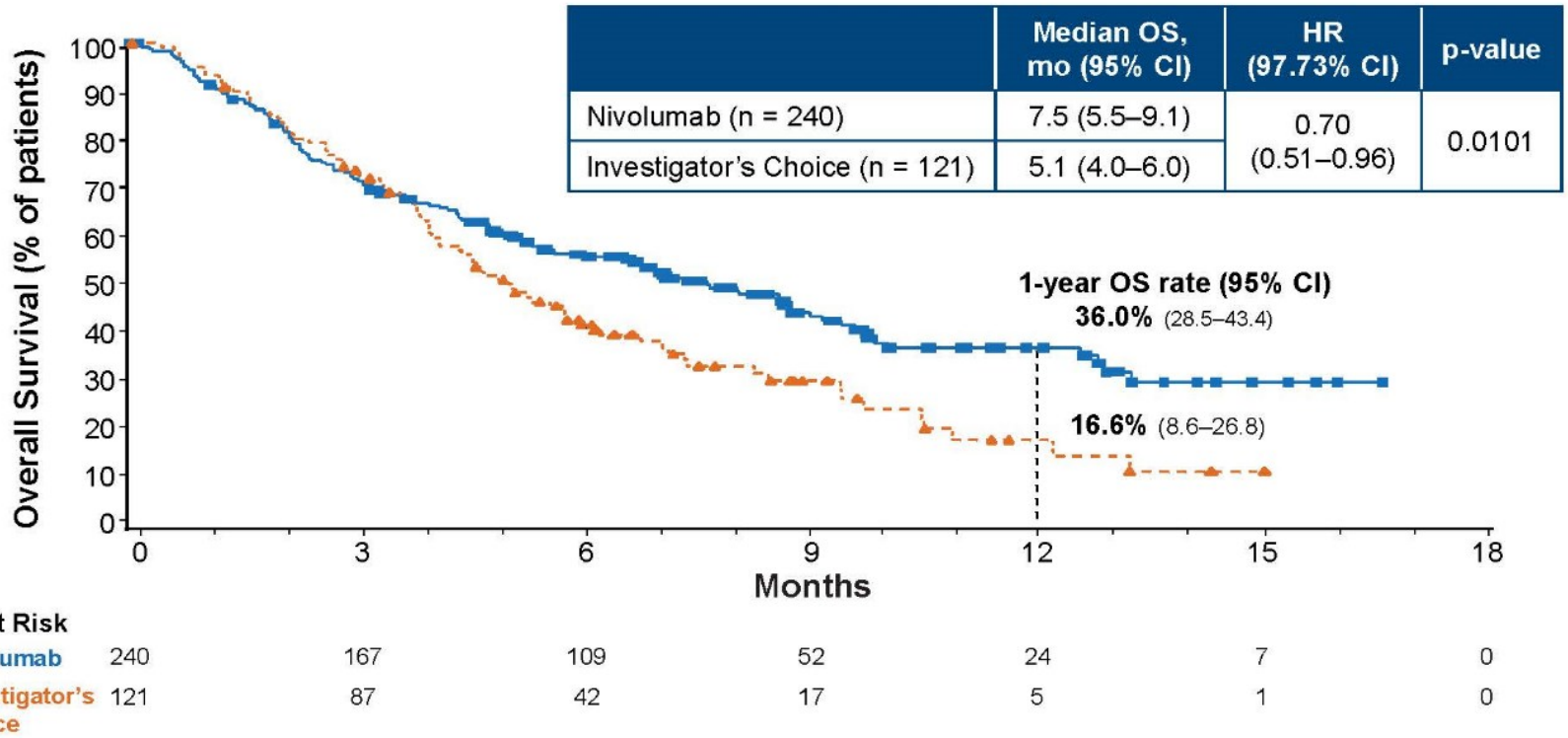
	CheckMate 141
Primary outcomes	Overall survival (OS) Defined as the time from randomisation to date of death from any cause. Survival time for patients who had not died was censored at the last known alive date. OS was censored at the date of randomisation for patients who were randomised but had no follow-up.
Secondary outcomes	Progression-free survival (PFS) Defined as the time from randomisation to first date of documented progression, by the investigator (as per RECIST 1.1 criteria), or to death due to any cause, whichever occurred first. Objective response rate (ORR) Defined as the proportion of randomised patients who achieved a best overall response (BOR) , complete response (CR) or partial response (PR), based on RECIST 1.1 criteria, as per investigator assessment
Exploratory endpoints	•Duration of response (DOR) DOR was defined as the time between the date of first confirmed response (CR or PR) to the date of the first documented progression as determined by the investigator (per RECIST 1.1), or death due to any cause, whichever occurred first. •Time to response (TTR) Defined as the time from randomisation to the date of the first response (CR or PR), as assessed by the investigator. TTR was evaluated for responders (i.e. patients with a BOR of confirmed CR or PR) only •Safety •Patient-reported outcomes (PROs) assessed using EORTC QLQ-C30 and QLQ-H&N35 questionnaires, as well as the EQ-5D-3L

Equivalency in OS of comparators

- Clinical expert opinion is that the taxanes (docetaxel and paclitaxel) and methotrexate have similar efficacy in terms of OS although differences in safety profiles exist. However, there is limited direct evidence from clinical trials that assess relative efficacy of docetaxel, methotrexate and paclitaxel versus one another or nivolumab or even against best supportive care (noted in BAHNO 2011 guidelines).
- ITT results from the IC arm of CheckMate 141 are therefore considered applicable to all three comparators included in this appraisal
- Clinical evidence for the safety and efficacy of nivolumab versus docetaxel and methotrexate presented from the RCT, CheckMate 141 which included both of these therapies as part of the IC of therapy arm
- Cetuximab (monotherapy) is also included in the IC arm of CheckMate 141 but not believed to be routinely used in UK clinical practice. Inclusion of cetuximab as part of IC arm in the CheckMate 141 trial reflects global nature of the trial and highlights the lack of a single, universally-accepted therapy for the treatment of platinum-refractory R/M SCCHN internationally.

Primary efficacy results

CheckMate 141 met primary endpoint with Nivolumab demonstrating significant improvements in OS relative to IC arm (HR 0.70 [97.73% CI, 0.51 to 0.96; p=0.0101]), corresponding to a 30% reduction in the risk of death with nivolumab versus IC of therapy



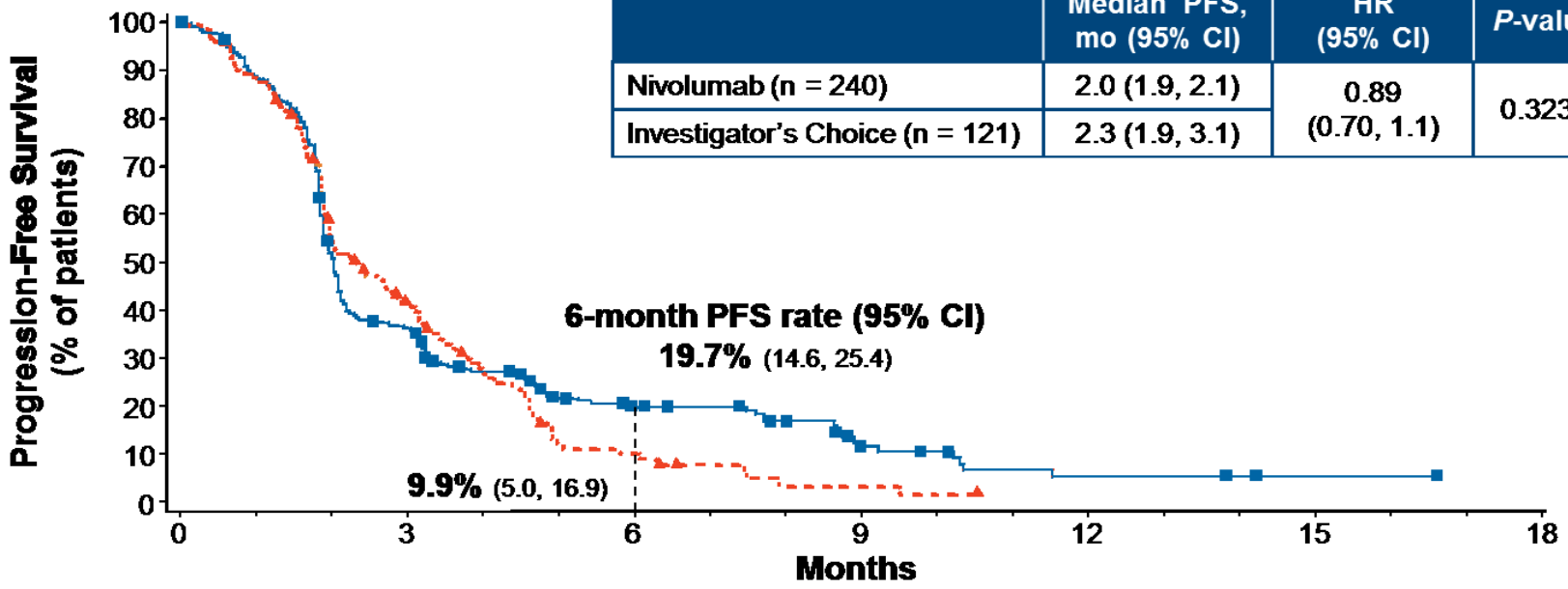
	Median OS, mo (95% CI)	HR (97.73% CI)	p-value
Nivolumab (n = 240)	7.5 (5.5–9.1)	0.70 (0.51–0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0–6.0)		

Abbreviations: CI: confidence intervals; HR: hazard ratio; OS: overall survival.
Source: Gillison et al. (2016)

Secondary efficacy results-PFS

Median PFS was similar between treatment arms; however, a delayed separation of Kaplan-Meier curves in favour of nivolumab was observed (HR, 0.89; 95% CI, 0.70, 1.1; p=0.3236)

	Median PFS, mo (95% CI)	HR (95% CI)	*P*-value
Nivolumab (n = 240)	2.0 (1.9, 2.1)	0.89 (0.70, 1.1)	0.3236
Investigator's Choice (n = 121)	2.3 (1.9, 3.1)		



Abbreviations: CI: confidence intervals; HR: hazard ratio; PFS: progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Ferris et al. (2016)9

Outcome summary table

Outcome	Nivolumab (n=240)	IC (n=121)
Overall Survival		
Deaths, n (%)	133 (55.4)	85 (70.2)
Median OS, months (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
HR for death with nivolumab (97.73% CI; p-value)[b]	0.70 (0.51, 0.96; p=0.0101)	
1-year survival rate, % (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)
Progression-free survival		
Events, n (%)	190 (79.2)	103 (85.1)
Median PFS, months (95% CI)	2.0 (1.9, 2.1)	2.3 (1.9, 3.1)
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)	
6-month PFS rate, % (95% CI)	19.7 (14.6, 25.4)	9.9 (5.0, 16.9)
Tumour response		
ORR, n (%) [95% CI]	32 (13.3) [9.3, 18.3]	7 (5.8) [2.4, 11.6]
Median TTR, months (range)	2.1 (1.8–7.4)	2.0 (1.9–4.6)

Abbreviations: CI: confidence intervals; HR: hazard ratio; IVRS: interactive voice response system; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumours; TTR: time to response.
Source: Gillison et al. (2016), Ferris et al. (2016) and CheckMate 141 CSR (7th June 2016)

Patient-reported HRQoL outcomes

Patient-reported outcomes evaluated using the EORTC QLQ-C30 and head-and-neck-specific module (QLQ-H&N35), with clinically meaningful changes defined as a change from baseline of ≥10 points. Health problems and perceived health status also assessed using the EQ-5D-3L

EORTC QLQ-C30 & EORTC QLQ-H&N35

- At baseline, no meaningful differences in both scale scores between the nivolumab and IC arms
- Significant differences between treatment arms observed in favour of nivolumab at both Weeks 9 and 15 compared to IC arm for some functional domains and symptoms.
- Time to deterioration was significantly delayed for nivolumab versus IC for some functional domains and symptoms

EQ-5D-3L

- During the first 21 weeks of follow-up, health problems were more prevalent in the IC arm relative to nivolumab, with a >10% difference in the percentage of patients reporting health problems for self-care at Week 9; for mobility, self-care, pain/discomfort, and anxiety/depression at Week 15; and for mobility, usual activities, and pain/discomfort at Week 21.

Sub-group analysis

- Exploratory subgroup analyses conducted in CheckMate 141 included OS by treatment group and:
  - PD-L1 expression (≥1% or <1%)
  - HPV-p16 status (positive or negative)
  - Selected baseline characteristics, including age (<65 or ≥65 to <75 or ≥75), Eastern Cooperative Oncology Group (ECOG) performance status (0 or ≥1), tobacco use (current/former or never), prior lines of systemic therapy (1 or 2 or ≥3) and by intended choice of therapy for the IC arm (docetaxel, methotrexate or cetuximab)
- The company stated that nivolumab demonstrated reductions in the hazard rate of death versus IC, regardless of PD-L1 expression, HPV-p16 status and selected baseline characteristics, including intended therapy for the IC arm. Notably, with regards to PD-L1 expression, no further benefit in OS was reported at increasing levels of PD-L1 expression (≥5% and ≥10%).
- Overall, these results demonstrate that the improved efficacy of nivolumab versus IC of therapy is generalisable across all relevant subgroups of patients included in the CheckMate 141 trial.

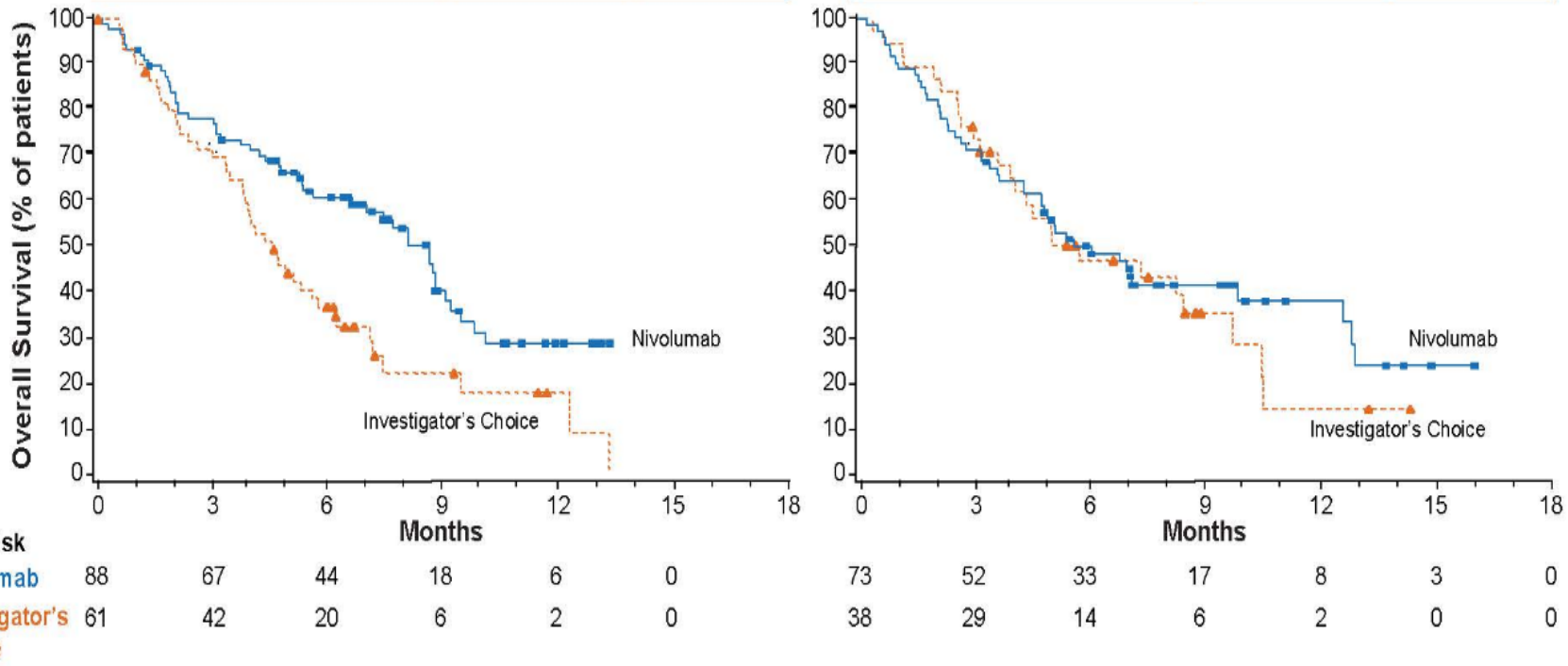
OS results by PD-L1 expression

PD-L1 Expression ≥ 1%

	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 88)	8.7 (5.7–9.1)	0.55 (0.36–0.83)
Investigator's Choice (n = 61)	4.6 (3.8–5.8)	

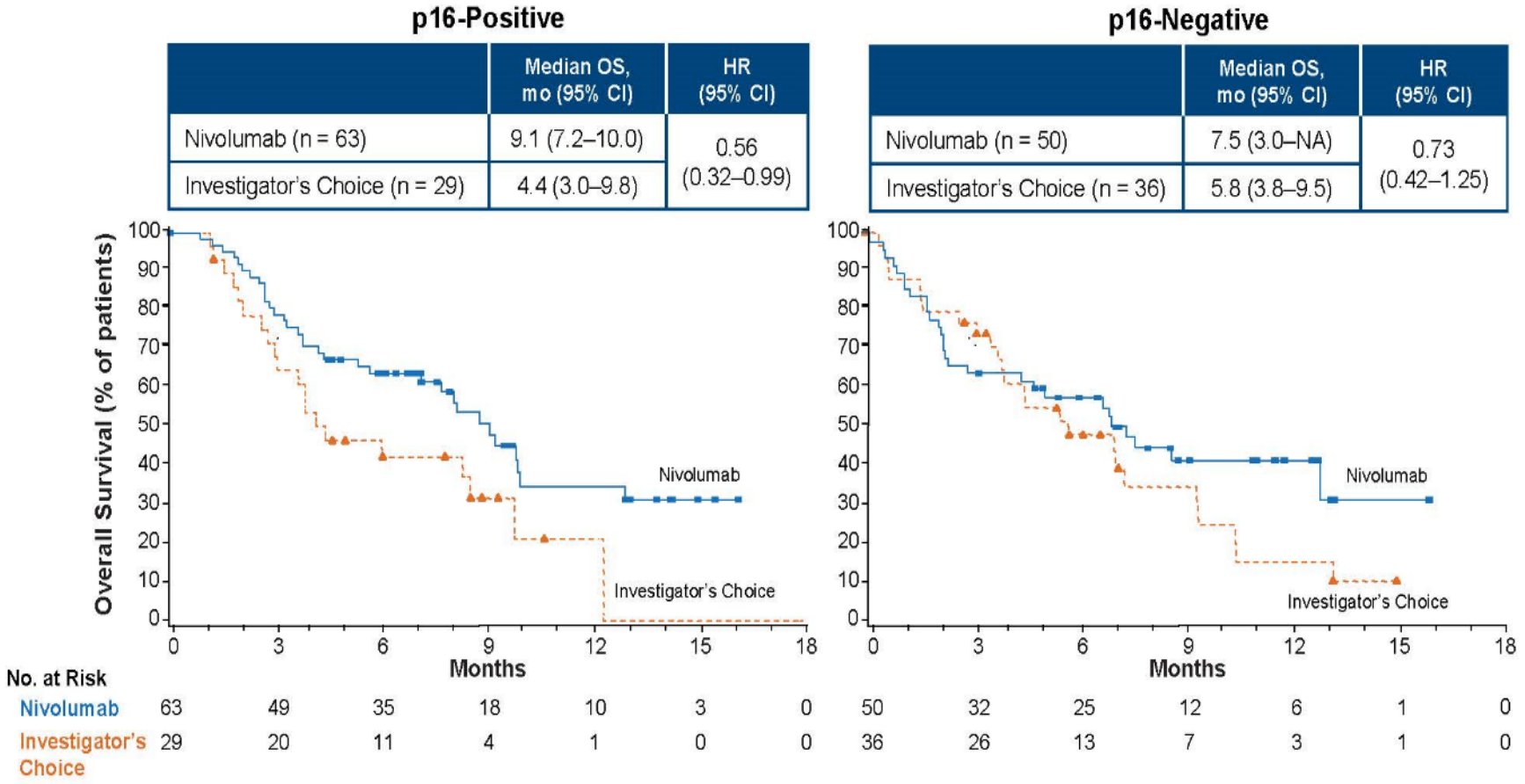
PD-L1 Expression < 1%

	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 73)	5.7 (4.4–12.7)	0.89 (0.54–1.45)
Investigator's Choice (n = 38)	5.8 (4.0–9.8)	



Company's submission – figure 15, page 70

OS results by HPV-p16 status



Company's submission – figure 16, page 71

Meta-analysis and indirect comparisons

- Evidence for the efficacy of nivolumab versus docetaxel and methotrexate is available directly from the CheckMate 141 trial.
- Review of the publications from both the original and the updated SLRs (see Section 4.1 of the CS) did not identify any randomised trials (in addition to CheckMate 141) in patients with platinum-refractory R/M SCCHN that investigated the use of comparators included in this appraisal versus one another or nivolumab or a common comparator therapy. As such, an indirect comparison between nivolumab and the therapies included as comparators for this appraisal was not considered appropriate for this submission

Adverse events

Adverse event, n (%)[b]	Nivolumab (n=236)		IC (n=111)	
Deaths	132 (55.9)		78 (70.3)	
Deaths due to study drug toxicity	2 (0.8)[c]		0[d]	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All causality AEs	229 (97.0)	97 (41.1)	109 (98.2)	58 (52.3)
Drug-related AEs	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
All-causality SAEs	127 (53.8)	66 (28.0)	66 (59.5)	36 (32.4)
Drug-related SAEs	16 (6.8)	11 (4.7)	17 (15.3)	12 (10.8)
All-causality AEs leading to treatment discontinuation	51 (21.6)	27 (11.4)	27 (24.3)	12 (10.8)
Drug-related AEs leading to treatment discontinuation	9 (3.8)	6 (2.5)	11 (9.9)	7 (6.3)

- Treatment discontinuations due to any grade AE (all causality) were similar between groups (21.6% nivolumab versus 24.3% IC), but proportions were lower in the nivolumab arm compared to IC of therapy (3.8% versus 9.9%) for drug-related AEs of any grade
- The most frequently reported AEs of any cause in the nivolumab arm were (any grade): fatigue (26.3%), nausea (19.1%), anaemia (18.6%), decreased appetite (18.6%), malignant neoplasm progression (18.2%), and constipation (15.3%); and (Grade 3-4): anaemia (5.9%), dyspnoea (5.5%), hyponatremia (4.7%), dysphagia (3.8%), and pneumonia (3.8%)
- Two deaths were reported in the nivolumab arm that were considered to be related to study drug toxicity (Grade 3 pneumonitis and Grade 5 hypercalcaemia)
- No new safety concerns with nivolumab were identified in CheckMate 141, with a similar safety/tolerability profile observed to that seen in trials of nivolumab monotherapy in other cancer types

Summary of ERG critique
clinical effectiveness (1)

- Mismatch between population referenced in anticipated indication for nivolumab as treatment for R/M SCCHN and CheckMate 141. According to the response to the clarification letter, the ERG understands that the company believes that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy, which is consistent with the inclusion criteria for the trial.
- CheckMate 141 has some significant limitations:
  - Study lacks comparison with one of the comparators in the NICE scope, paclitaxel
  - Study did not include comparisons with comparators specified in NICE scope, but with IC, which permits clinician choice of treatment. This therefore means that intention to treat (ITT) analysis prevents an unbiased estimate of the effectiveness of nivolumab versus any of the comparators. Furthermore IC may might be considered an unbiased estimate versus standard care, but only if IC was made on the same basis as that in clinical practice which is impossible to know.
  - Study includes a comparator not specified in the NICE scope, cetuximab.

Summary of ERG critique
clinical effectiveness (2)

- Quality assessment of CheckMate 141 identified issues that could influence the validity of the findings of the trial such as lack of blinding as well as imbalances in the drop-outs between treatment and comparator. In addition, results were prone to bias as the trial was open label and clinicians were able to exercise their own judgment in both concomitant and subsequent treatment
- ERG further identified two issues which might limit the generalisability of results of the CheckMate 141 trial
  - Based on information in the CS and the response for request for clarification, the prevalence of males in the index population is approximately 70%. It should be noted that 83.1% of the trial population is male. Given that discrepant results are reported for OS (nivolumab versus IC; HR 0.65 (95% CI 0.48 to 0.88) and 0.93 (95% CI 0.47 to 1.85) for males and females, respectively), this issue might influence the applicability of study results to the overall UK population.
  - The ERG noticed differences in the OS HRs between participants from North America and the European Union (EU), i.e. 0.55 (95% CI 0.36 to 0.85) and 0.91 (95% CI 0.62 to 1.33), respectively. In response to request for clarification, the company offered several explanations, including the lower proportion of human papillomavirus (HPV)-positive and never smoker patients in Europe, an imbalance of HPV status across treatment arms within the European subgroup and differences in choice of IC of therapy. Differences in the recorded baseline characteristics between the EU and North America as well as in the treatments chosen highlights the potential for lack of applicability to the UK

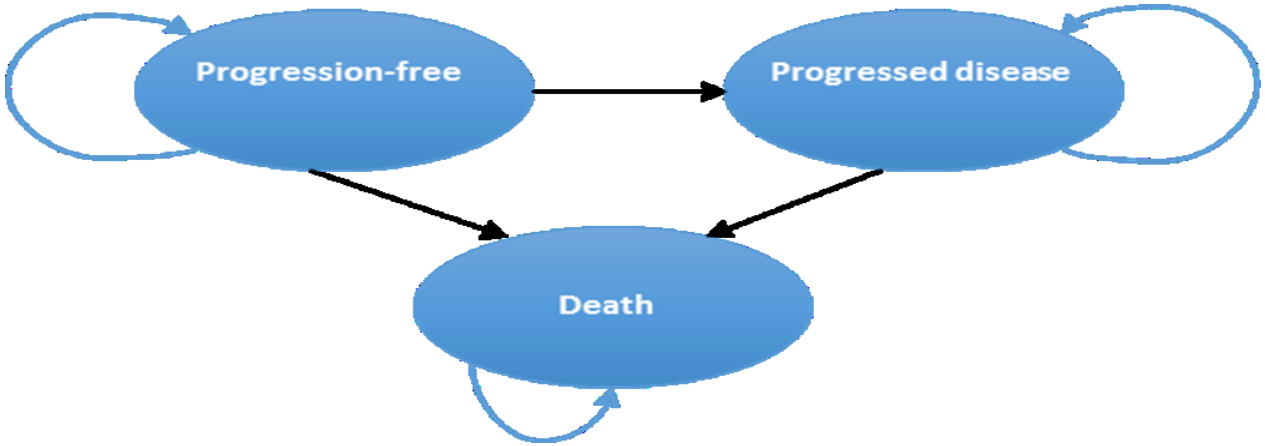
Summary of ERG critique
clinical effectiveness (3)

- ERG agreed that nivolumab resulted in a statistically significant reduction in the hazard rate for OS at the 5% level. However, variation by individual therapy with nivolumab was noted with nivolumab performing particularly well versus cetuximab (HR=*****) as opposed to versus docetaxel (HR=*****). A request to repeat analyses excluding cetuximab at clarification demonstrated little effect of the removal of the cetuximab patients (expected given the small number (n=15) of patients who received cetuximab treatment). Results showed there was no change in terms of statistical significance, but a ********** in the advantage of nivolumab versus IC from a HR (97.73% CI) of 0.70 (0.51, 0.96; p=0.03236) to **********.
- The ERG noted that, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab. Also, the response to a clarification question regarding the difference in the HR for OS between the EU and North America highlighted the difference in percentage receiving each of the treatments in the scope (docetaxel and methotrexate). The ERG would therefore conclude that, whilst it is reasonable to believe that nivolumab extends life expectancy, it is impossible to be confident by how much in comparison to any treatment in the scope or which is considered to be standard care in the UK.
- The ERG raised concerns regarding use of subsequent therapies and imbalances between nivolumab and IC arms. Exploratory analysis with simple censoring of any patient who had received subsequent systemic cancer therapy were requested at the clarification stage (see question A3) . The results from these analyses demonstated that the HR of death for nivolumab versus IC (**********) were ********** to that observed in the primary analysis of OS (0.70; 0.51, 0.96), suggesting that the treatment effect of nivolumab versus IC is ********** **********

Cost-effectiveness evidence

company submission chapter 5

Company's model
(Cohort-based partitioned survival model – 3 states)



Factor	Chosen values	Justification
Time horizon	20 years	Time horizon is sufficiently long enough for >99% of patients in the model to have died
Cycle length	4 weeks	From Week 9 of the CheckMate 141 trial tumour assessments performed every 6 weeks. Dosing of nivolumab every 2 weeks and comparators dosing ranges from once weekly to once every three weeks. 4-week cycle length chosen as pragmatic consideration of these factors.
Half-cycle correction	Yes	Mitigate bias due to cycle length

Model details and clinical data

- Population reflects characteristics of patients in Checkmate 141, that is patients with R/M SCCHN who had progressed after platinum-based therapy.
- Nivolumab compared with investigator choice (IC) of treatment of either docetaxel, methotrexate or paclitaxel to reflect lack of a single, universally-accepted therapy for the treatment of R/M SCCHN and distribution of therapies used in UK clinical practice.
  - Clinical data from the IC arm of CheckMate 141 used for the comparison of nivolumab to paclitaxel. Docetaxel and paclitaxel both taxanes and often grouped together in discussion of clinical agents for the treatment of R/M SCCHN .The clinical systematic literature review identified limited RCT evidence for paclitaxel as a monotherapy for the treatment of platinum refractory R/M SCCHN (see Section 4.1 of the CS), thereby necessitating an assumption of equivalence to docetaxel in order to model this comparator.
  - Clinical equivalence between these therapies with regards to efficacy in patients with platinum-refractory R/M SCCHN has been confirmed by expert clinician feedback and is supported by data from a phase II clinical trial.
  - Estimated OS, PFS and time to duration (TTD) based on data from the IC arm were assumed to be applicable to docetaxel, methotrexate and paclitaxel (i.e. assuming equivalence among these treatment)
- Clinical parameters in the model (e.g. OS and PFS) based on patient-level ITT data from the treatment arms of CheckMate 141 trial (i.e. nivolumab and IC)
- Number of patients in each state was derived directly from the cumulative survival probabilities for progression free survival (PFS) and overall survival (OS).
- TTD data from CheckMate 141 used to provide accurate estimate of duration of therapy in the model and to account for the possibility that some patients may continue to receive treatment with nivolumab beyond disease progression.
  - This was to take into account the possibility that some patients may experience an unconventional immune-related response (see Section 2.1 of the CS), as is characteristic of immune-checkpoint inhibitors and to provide a realistic estimation of treatment related costs based on actual treatment duration.

Extrapolation of clinical data in the model

- Multiple parametric time-to-event models were used to estimate OS, PFS and TTD in accordance with NICE Decision Support Unit (DSU) guidance to estimate proportion of patients in each health state across the time horizon of model.
- For all three outcomes (OS, PFS and TTD), proportional hazards assumption did not hold (see CS Figures 23, 30 and 37; non-parallel curves that cross/overlap). Therefore, the company estimated all time-to-event models independently for nivolumab and IC.
- For each outcome, company used the same statistical distribution in each treatment arm based on statistical fit, visual inspection and clinical plausibility.
- Clinical plausibility of extrapolated models was based on expert clinical opinion and comparison with trial data for nivolumab from other indications over a longer follow-up than CheckMate 141. Clinical feedback proposed that data from squamous NSCLC trials could be used due to similarity between the two indications in terms of tumour histology, patient characteristics, prognosis etc.
- For the IC arm, survival estimates from expert clinical opinion gathered at an international advisory board and from UK clinicians were used to validate the estimates predicted by the distributions used in the company's base case.

Estimated mean OS, PFS and TTD in months (over a time horizon of 20 years)

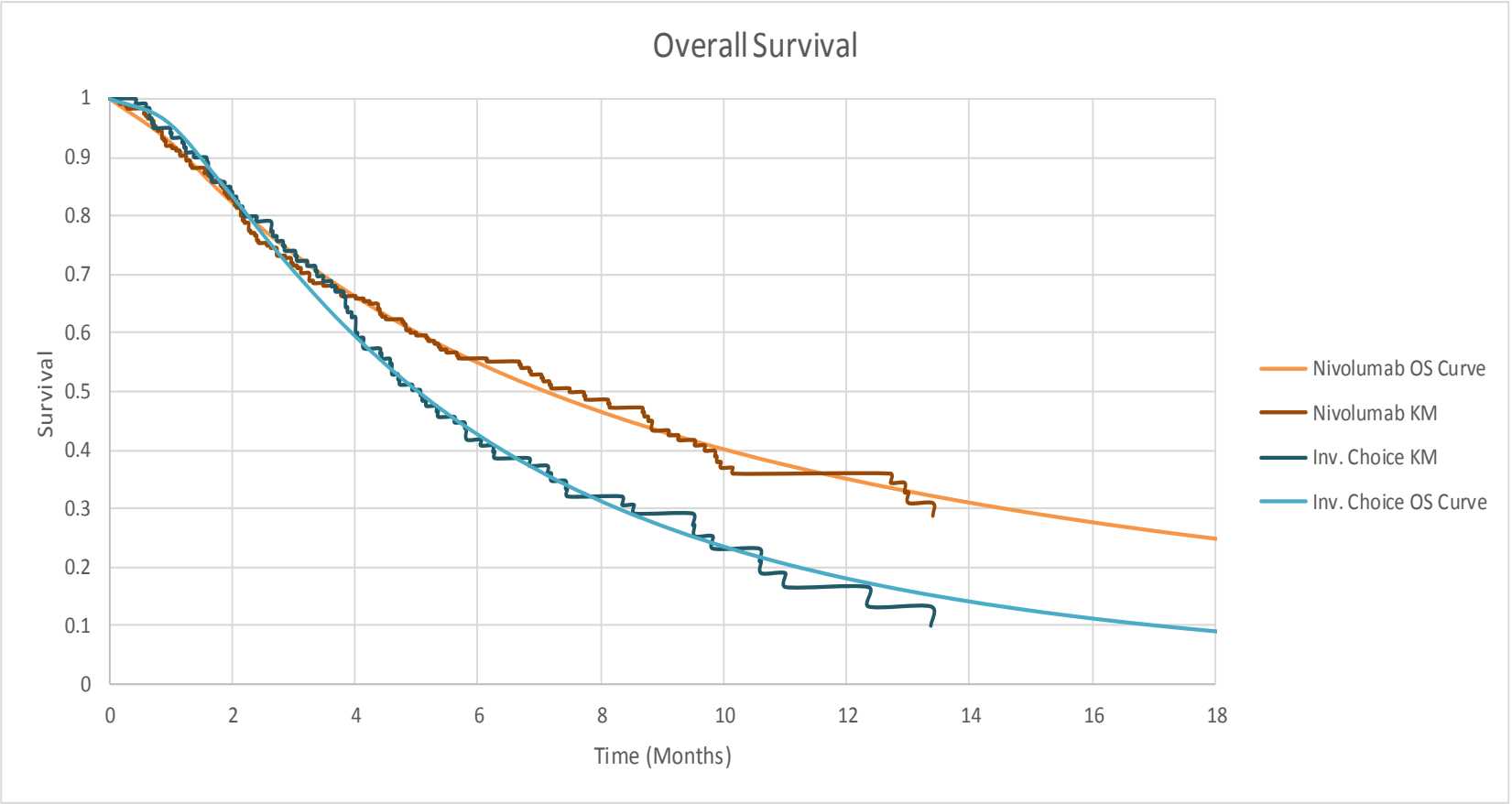
	Mean OS (months)		Mean PFS (months)		Mean TTD (month	
Distribution	**Nivolumab**	**IC**	**Nivolumab**	**IC**	**Nivolumab**	**IC**
Exponential	11.2	7.8	[b]	[b]	[b]	[b]
Weibull	11.2	7.0	[b]	[b]	[b]	[b]
Gamma	11.0	7.1	[b]	[b]	****b,c	3.3[b,c]
Gompertz	21.0	6.9	[b]	[b]	b	[b]
Log-normal	17.7	8.4	4.3	3.7	b	[b]
Log-logistic	18.7	9.1	4.3	3.9	****	3.6
Generalised-gamma	18.6	7.6	4.6	3.6	****	3.3
Spline models:						
1-spline hazard	[a]	[a]	[b]	[b]	b	[b]
1-spline odds	[a]	[a]	[b]	[b]	b	[b]
1-spline normal	[a]	[a]	[b]	[b]	b	[b]
2-spline hazard	[a]	[a]	[b]	[b]	b	[b]
2-spline odds	[a]	[a]	9.2	3.7	****d	3.3[d]
2-spline normal	[a]	[a]	7.6[b,c]	3.6[b,c]	****	3.3

Note: The company preferred option is shaded in grey; The spline models were not considered relevant given that the added complexity was not justified based on the goodness-of-fit statistics; [b] This distribution was not considered relevant by the company; [c] Added by the ERG as this distribution had the best goodness-of-fit statistics for at least one treatment; [d] Corrected by the ERG (recalculated based on the economic model submitted by the company)

CS = company submission; ERG = Evidence Review Group; IC = investigator's choice; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation

Overall survival parametric fitting

Kaplan-Meier and log-normal curves



CS = company submission; IC = investigator's choice; KM = Kaplan Meier; OS = overall survival

Company model inputs:
health-state utilities

- No published, UK-specific utility data using methods preferred by NICE identified by HRQoL systematic literature review (SLR) .
- One potential study identified in which utilities were derived from members of the Canadian general public using the standard gamble approach for a variety of health states related to head and neck cancer including recurrent or metastatic disease (see CS Appendix 10). Therefore, utility data from CheckMate 141 trial considered to be most relevant to the decision problem for this appraisal.
- Treatment-dependent health state utilities for the progression-free and progressed disease states were derived from the EQ-5D-3L data collected from patients in the CheckMate 141 trial as below:

Health state	Nivolumab		IC of therapy		Overall	
	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]
Progression-free	***	********** **********	***	********** **********	***	********** **********
Progressed disease	***	********** **********	***	********** **********	***	********** **********

Company model inputs:
Adverse event utility decrements

Utility decrements applied separately for each AE and only once during the first cycle of the model based on proportion of patients in each treatment arm experiencing each AE (see CS section 5.3.6).

Due to lack of published disutility values for AEs in SCCHN, disutility estimates were obtained from studies and previous technology appraisals (TA) reporting disutility estimates from patients with advanced lung cancer and gastrointestinal malignancies particularly TA 172 (see CS Table 41). Utility data from these indications was validated by a UK clinical expert.

No disutility value was available for hyponatraemia, and a disutility of zero was assumed. No disutility was reported for anaemia; this disutility estimate was assumed to be the same as that of fatigue, based on expert clinical opinion.

Disutilities of adverse events included in the model :

Adverse event	Disutility	Source
Fatigue	-0.07346	Derived from published study in advanced lung cancer Nafees *et al.* (2008)
Dyspnoea	-0.05	Derived from published study in advanced lung cancer Doyle *et al.* (2008)
Hyponatraemia	0	Assumption
Anaemia	-0.07346	Nafees *et al.* (2008)-assumed to be same as fatigue
Neutropenia	-0.08973	Nafees *et al.* (2008)
Dysphagia	-0.04802	Assumed to be the same as for nausea and vomiting
Nausea and vomiting	-0.04802	Nafees *et al.* (2008)
Anorexia	-0.153	Based on NICE TA378

Company model inputs: resource use and costs

- Drug acquisition costs were obtained from the British National Formulary (BNF, 2016) for nivolumab and from the electronic market information tool (eMit, 2015) for generic comparator products.
- Weight based dosing using normal distribution for weight derived from the mean and standard deviation values from CheckMate 141 was used.
- Drug wastage (i.e. no vial sharing) was assumed for all therapies in order to be conservative about the expected cost of nivolumab.
- Dose intensity reduction was calculated based on the proportion of doses received that were delayed in CheckMate 141. Calculation for dose intensity relied on assumption that a dose delay was equivalent to a single missed dose for nivolumab (Q2W), methotrexate or docetaxel (QW for both). Drug acquisition costs were therefore adjusted to account for the reduced dose intensity received by patients in CheckMate 141 due to dose delays. It was assumed that the drug would not be prepared for these dose delays and that a cost would therefore not be incurred by the NHS.
- Dosing frequency used in the company base case (30 mg/m2,QW)was chosen to ensure consistency with the trial regimen from which efficacy and safety inputs for the model were derived. However, frequency of docetaxel that is most routinely used in UK clinical practice is 75 mg/m2, once every 3 weeks.
- Drug administration and monitoring costs for nivolumab and comparators were derived from the NHS reference cost schedule 2014–15.
- All therapies included in the model were intravenously-administered and assumed to incur same administration costs. Similarly, the type and frequency of monitoring visits were assumed to be the same for all patients included in the model who were receiving initial systemic therapy

Company model inputs:
Subsequent systemic therapy

- In company base case analysis, proportion of patients who discontinued initial treatment in the model were assumed to receive subsequent systemic anti-cancer therapy, with costs accrued accordingly. This was based on clinical trial data from CheckMate 141(nivolumab ***** and IC *****, see CS Table 46).
- A number of assumptions were made:
  - Given the advanced nature of the disease, patients are not expected to receive more than one subsequent systemic therapy post-discontinuation.
  - The company assumed that patients would receive subsequent therapy for a median of 1.9 months (justified by the median duration of therapy for patients in the IC arm of CheckMate 141)
  - Patients who had received either docetaxel or paclitaxel were not treated with another taxane.
  - Patients in the UK are not expected to receive either nivolumab or paclitaxel as subsequent systemic therapy so the model restricts the choice of post-discontinuation therapies to docetaxel and methotrexate
- Two scenario analyses were performed. In the first scenario analysis, the proportion of patients receiving subsequent therapy was reduced to 12% in both treatment arms (see CS Scenario 17; Section 5.8.3), based on the market research on the proportion of patients expected to receive later-line therapy for R/M SCCHN. Additionally, the cost of subsequent systemic therapy was excluded from the model (see CS Scenario 18; Section 5.8.3).

Company's base case results

deterministic results with discounted price for nivolumab

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	********	1.33	*****				
Docetaxel	12,538	0.65	0.37	******	0.68	*****	£34,902
Paclitaxel	12,603	0.65	0.37	******	0.68	*****	£34,777
Methotrexate	12,535	0.65	0.37	******	0.68	*****	£34,908

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Model predictors of clinical outcomes compared with CheckMate 141:

Outcome, months (95% CI)	Nivolumab		Comparators*	
	CheckMate 141	Economic model	CheckMate 141	Economic model
PFS				
Median	2.0 (1.9, 2.1)	2.6	2.3 (1.9, 3.1)	2.6
Mean	-	4.6	-	3.6
TTD				
Median	1.9 (1.6, 2.3)	3.0	1.9 (1.6, 2.0)	2.30
Mean	-	****	-	3.6
OS				
Median	7.5 (5.5, 9.1)	7.1	5.1 (4.0, 6.0)	5.0
Mean	-	17.7	-	8.4

Abbreviations: CI: confidence intervals; IC: investigator's choice; OS: overall survival; PFS: progression-free survival; TTD: time to discontinuation

Disaggregated base case results

- Nivolumab is more effective than docetaxel, methotrexate and paclitaxel in terms of both QALYs and LYs.
- Main source of QALY and LY benefit with nivolumab treatment came from an extension in the period of time spent in the PD state QALY. This is reflective of the improved OS for nivolumab versus IC (with relatively similar PFS), and the higher utility associated with nivolumab treatment in the PD state as a result of treatment continuing post progression.
- Nivolumab was also associated with higher life time costs than docetaxel, methotrexate and paclitaxel

QALY and LY by health state:

Health state				
	Nivolumab QALYs	**IC QALYs**	**Incremental QALYs**	**% of total increment**
PF	******	0.18	*****	15%
PD	******	0.22	*****	83%
AE disutility	******	-0.03	*****	2%
Total	******	0.37	*****	100%
	Nivolumab LYs	**IC LYs**	**Incremental LYs**	**% of total increment**
PF	0.34	0.26	0.09	13%
PD	0.99	0.39	0.60	87%
Total	1.33	0.65	0.68	100%

AE = adverse event; CS = company submission; IC = investigator's choice; LY, life year; PD = progressive disease; PF = progression-free; QALY = quality-adjusted life year

Company's deterministic and probabilistic sensitivity analyses

Probabilistic sensitivity analyses (PSA)

Probabilistic ICERs slightly higher than the company's deterministic base case:

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)
Nivolumab	********	*******			
Docetaxel	12,569	0.37	********	********	£34,914
Paclitaxel	12,710	0.37	********	********	£34,807
Methotrexate	12,626	0.37	********	********	£34,644

Based on pairwise comparisons of nivolumab versus the comparators, the company reported a 70% probability of nivolumab (with PAS) being cost effective at a threshold of £50,000 per QALY.

Deterministic sensitivity analyses (DSA)

Company conducted DSA by varying all parameters for which there were single input values into the model by ±15% of their mean value in order to identify key model drivers.

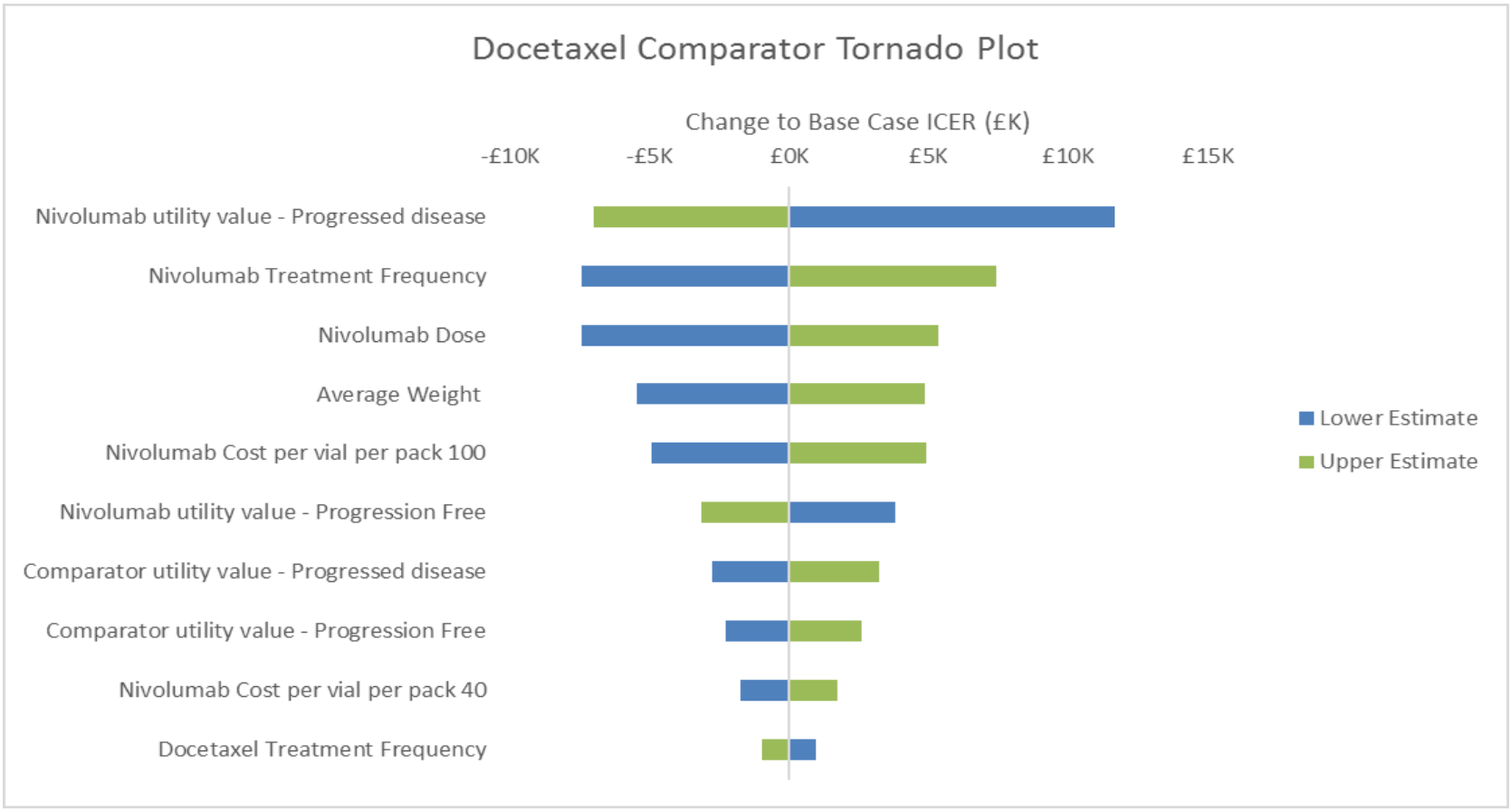
DSA results are presented using tornado diagrams with the top 10 drivers of cost effectiveness in CS. (see figures 57-59, pages 162-165)

Parameter driving the model the most is the utility value utilised for patients in the progressed disease state in the nivolumab arm (causing an increase in the ICER of *********)

Following this, the most influential parameters are the treatment frequency of nivolumab and the nivolumab dose.

Company's DSA:

tornado diagram of the ten most influential parameters: nivolumab versus docetaxel (with PAS for nivolumab)



Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme

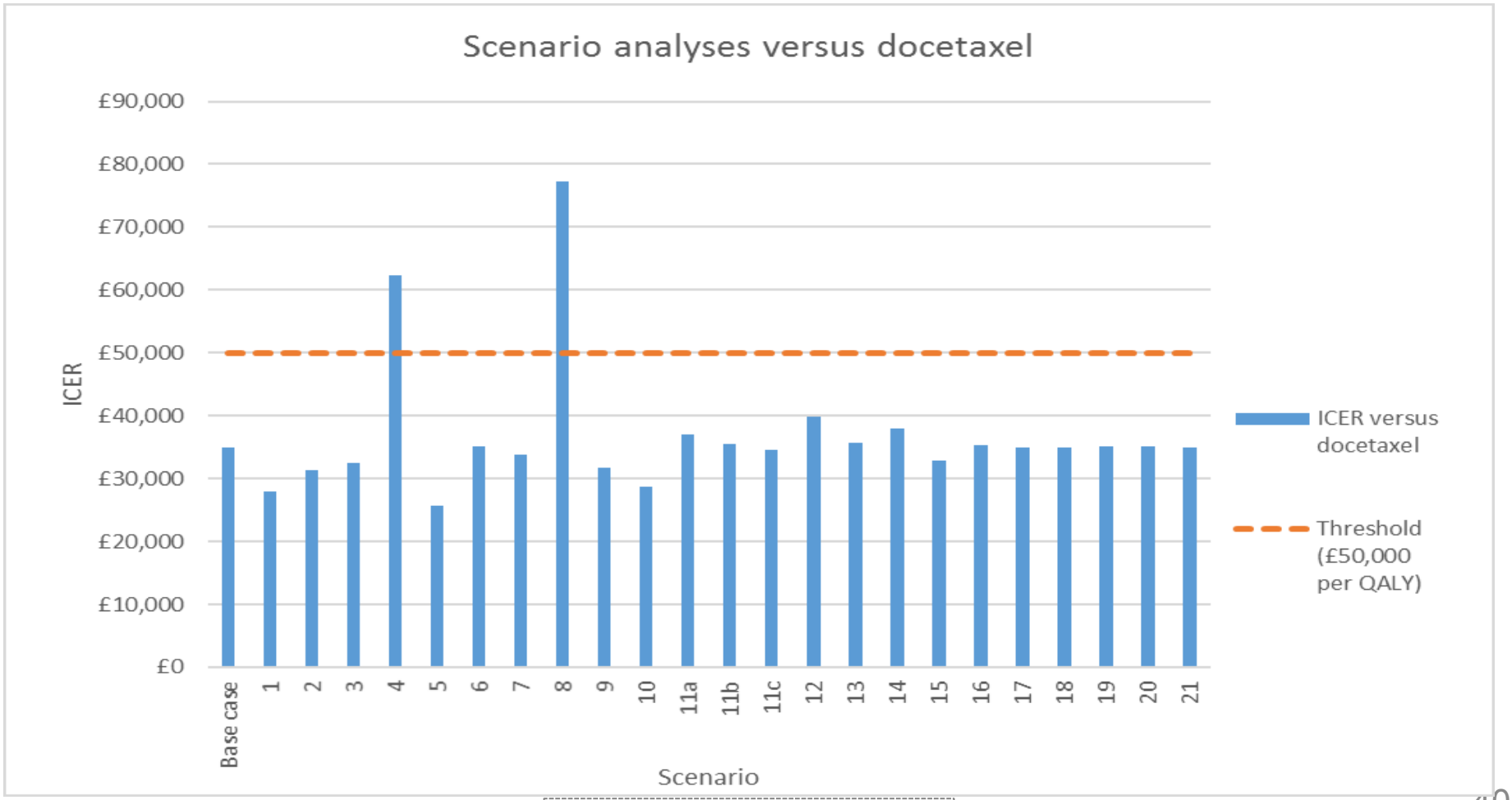
Company's scenario analyses

Scenario	Description	Signpost CS
1-3	Alternative clinical stopping rules imposed at 1, 2 and 3 years	Tables 65 and 66
4-9	Alternative parametric survival distributions for OS, PFS and TTD	Tables 67-72
10	Using PFS to model time on treatment rather than TTD; assuming no treatment beyond progression	Tables 73 and 74
11a–c	Alternative time horizons of a) 10 years, b) 15 years and c) 25 years	Tables 75 and 76
12	Using treatment independent health-state utilities	Tables 77 and 78
13	Using no disutility for AEs	Tables 77 and 78
14	Using Docetaxel 75 mg/m^2 Q3W dose for treatment costs	Tables 77 and 78
15	Permitting vial sharing; i.e. assuming no drug wastage	Tables 77 and 78
16	Using 100% dose intensity; i.e. assuming no dose delay	Tables 77 and 78
17	Using a reduced % of patients receiving subsequent systemic therapy; reduced by 12% based on market research	Tables 77 and 78
18	Using no subsequent systemic therapy costs	Tables 77 and 78
19	Using no terminal care cost	Tables 77 and 78
20	Using average weight and BSA from the overall trial population	Tables 77 and 78
21	Using average BSA from UK cancer patients	Tables 77 and 78

AE = adverse event; BSA = body surface area; CS = company submission; OS = overall survival; PFS = progression-free survival; Q3W = once every 3 weeks; TTD =progression-free survival; UK = United Kingdom

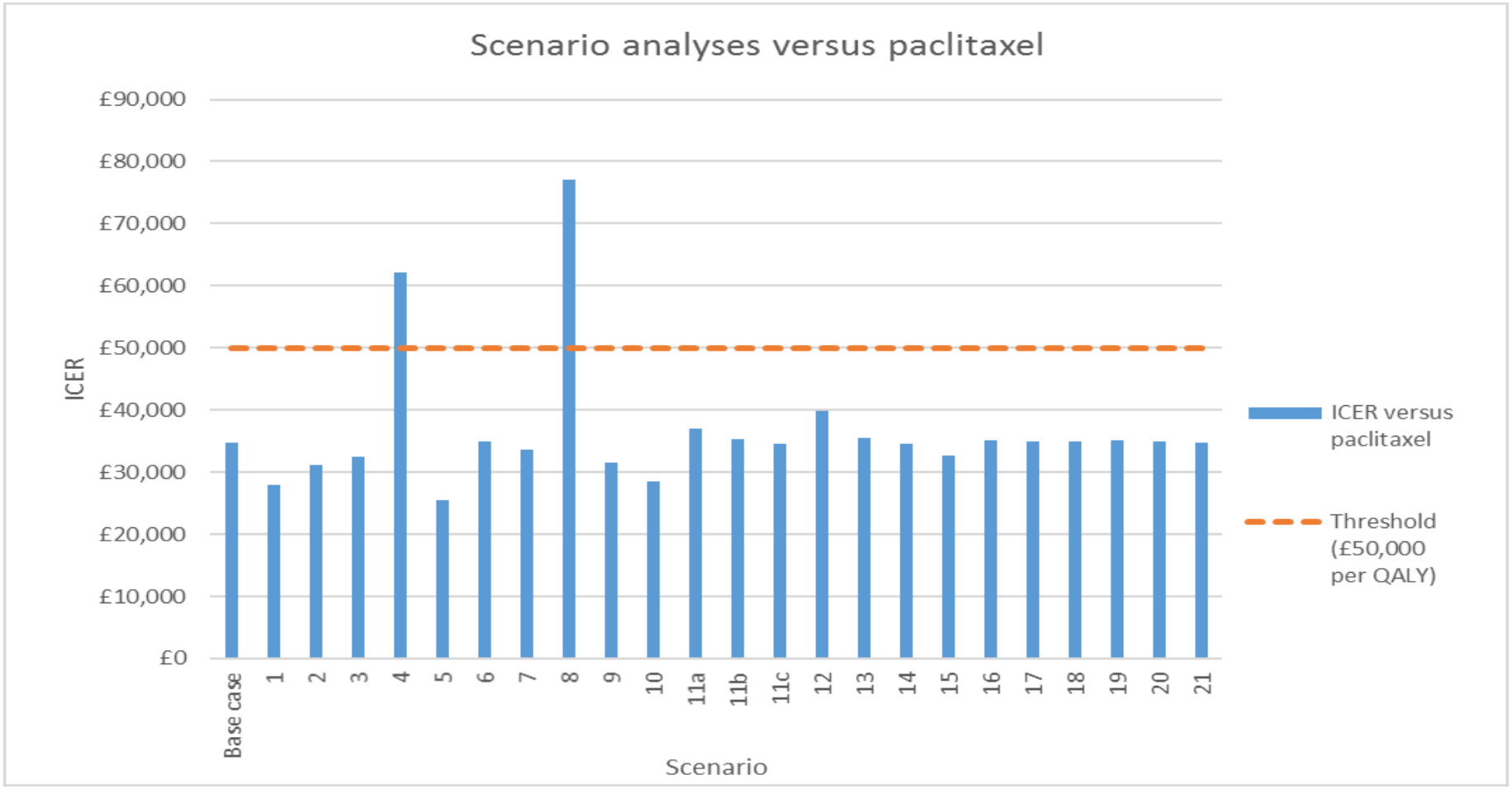
Company's scenario analyses: summary

Summary of results from scenario analyses (Scenarios 1–21): nivolumab versus docetaxel:



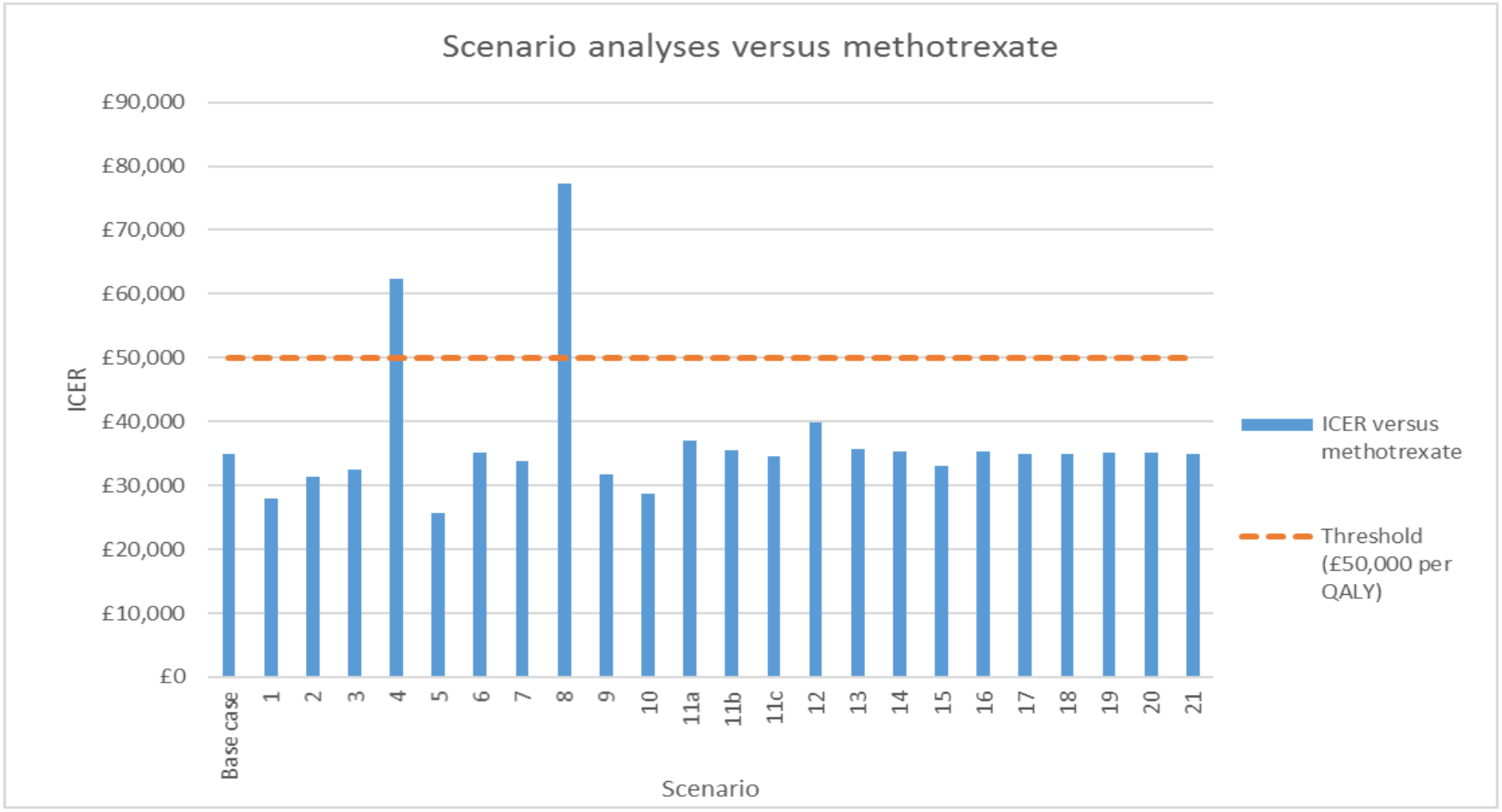
Company's scenario analyses: summary

Summary of results from scenario analyses (Scenarios 1–21): nivolumab versus paclitaxel:



Company's scenario analyses: summary

Summary of results from scenario analyses (Scenarios 1–21): nivolumab versus methotrexate:



Summary of ERG critique
cost effectiveness (1)

Strengths of the model

- Population represented in the model seems to correspond to the expected licensed indication and the final NICE scope.
- ERG considered the statistical methods used by the company for selecting the distributions for the time-to event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis.

Limitations of the model

- The equivalence assumption between the IC treatments is not supported by clinical evidence.
  - Docetaxel/ paclitaxel: The assumption is based on the opinion of two UK clinicians and from an international advisory board. The two UK clinicians emphasised the lack of evidence demonstrating a difference in effectiveness between docetaxel and paclitaxel. However the ERG noted that there was no empirical evidence to support the assumption.
  - Docetaxel/ methotrexate: A scenario analysis provided by the company (see clarification letter table 22), using treatment specific effectiveness estimates for docetaxel and methotrexate (instead of using IC effectiveness), showed that the assumption of equivalence between docetaxel and methotrexate is not likely to be influential in terms of incremental QALYs, incremental costs and the ICER.

Summary of ERG critique
cost effectiveness (2)

- The ERG raised concerns regarding interpretation and validation of time-to-event models selected by the company. The ERG agreed with the selection of the log-normal distribution for OS and generalised gamma for PFS in the company base case analysis but disputed the selection of the log-logistic distribution for TTD. Instead, the ERG used the generalised-gamma distribution in its base-case for two reasons:
  - PFS and TTD curves cross for the IC arm suggesting that there is post-progression treatment which seems implausible for the IC arm. Use of the generalised-gamma distribution resolves this issue.
  - Secondly, although there is no clear best option based on the goodness-of-fit statistics, based on visual inspection the ERG prefer the generalised-gamma as the tail seems more plausible.
- The ERG highlighted that health state utility data for *** of 361 patients **** were missing in the company base-case. In response to the clarification question B7, the company identified **** patients who had a baseline EQ-5D score but were not assigned to a health state at baseline and hence not included in the company base-case. The company repeated the calculation of utility values by therapy and by health including these **** patients, under the assumption that these patients were in the pre-progression health state at the time of the baseline measurement (consistent with the inclusion criteria). This resulted in progression free utility estimates that were lower for both nivolumab and IC and were included in the ERG's base-case analysis. Furthermore, it was unclear to the ERG whether the differences in utility between the treatments were due to differences between treatments or selection of cases (i.e. missing cases). Therefore, the ERG base-case used treatment independent utility values.
- The company was requested to carry out multiple imputation to adjust for missing data during clarification which resulted in an increase in the ICER's by about ****. The ERG agreed with the company's assertion that multiple imputations as applied in the response to clarification question B7c cannot be considered robust and therefore used the company's naïve imputation approach in its base case analysis.

Summary of ERG critique
cost effectiveness (3)

- Incorporating of adverse events only once in the first cycle might underestimate the long-term influence of AEs on the cost effectiveness outcomes. However it is expected to have a minor impact on the cost effectiveness results given the relatively small differences between treatments in rates of adverse events
- The ERG was unclear with regards to resource use and costs as to why the proportions of subsequent treatment was assumed to be treatment dependent. An average of the proportions of subsequent therapies from the CheckMate 141 trial was therefore used in ERG base-case instead.
- The administration schedule of docetaxel applied in the model is not representative of UK daily practice. Therefore, the ERG used the once every three week administration schedule of docetaxel (75 mg/m2 per administration) instead of the once weekly administration schedule (30 mg/m2 per administration) in its base-case analysis because this schedule is more routinely used in the UK and because there is no evidence to support a difference in efficacy between the two docetaxel schemes.
- The dosing schedule of nivolumab has recently been modified by the US Food and Drug Administration (FDA) from the 3 mg/kg every two weeks to a 240 mg fixed dose every two weeks for the treatment of renal cell carcinoma, metastatic melanoma and non-small cell lung cancer. The influence of this modified dosing scheme on the cost effectiveness results was explored by the ERG in an exploratory analysis.

ERG base case revisions
summary of changes

The ERG revised the company's base case as follows:

- Changing the standard deviation into standard error for utility scores in the probabilistic sensitivity analyses (PSA) . Standard deviation was incorrectly labelled as standard error in the model.
- Adverse events costs and disutility were added for pneumonitis.
- Dosing of docetaxel was changed to once every three weeks,75 mg/m^2 in accordance with UK clinical practice.
- Using generalised-gamma distribution for TTD instead of the log-logistic
- Using overall utility estimates given the uncertainty in the estimation of the treatment dependent utility scores from CheckMate 141 trial.
- Using treatment independent proportions for subsequent treatments.

ERG base case revisions
PSA results

	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
ERG base-case	Nivolumab	*********	****			
	Docetaxel	£10,276	0.41	*********	******	£49,848
	Paclitaxel	£11,732	0.41	*********	******	£46,611
	Methotrexate	£11,753	0.41	*********	******	£46,565

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

The cost effectiveness acceptability curves (see figure 5.9, page 110 of ERG report) show that nivolumab has a probability of being cost-effective of 13% and 53% at thresholds of £30,000 and £50,000 per QALY gained, respectively.

ERG additional exploratory analyses

- Assumption of nivolumab fixed dose of 240 mg every two weeks (independent of weight) based on the modification of the recommended dosage regimen for nivolumab by the FDA . Although this is currently not applicable to the present population, the impact of this dosage modification is explored.
  - Slightly increased ICERs versus nivolumab (with PAS) of £50,160 to £53,439
- Assumption of equivalence between docetaxel and paclitaxel to examine how much more effective paclitaxel would need to be (compared with docetaxel) in order to be cost effective compared with nivolumab.
  - The threshold analyses indicated that for paclitaxel to be cost effective compared with nivolumab (at a threshold of £50,000 per QALY), the HR for paclitaxel versus docetaxel should be no higher than approximately 0.93 (for both OS and PFS).
- Limiting extrapolation of treatment benefits by using shorter time horizons (two and five year. It is noteworthy that in the CS base-case the majority (83%) of the estimated QALY gain (87% of the estimated LY gain) is attributable to the period after disease progression has been confirmed (see sections 5.2.10 and 5.2.11). The lack of external validation of long-term outcomes hampers the interpretation of this extrapolation. Therefore, different time horizons were explored (in addition to the time horizons explored by the company in CS scenario analysis 11)
  - £91,687 to £98,925 (two year)
  - £59,984 to £63,833 (five year).

End of life

NICE End of life Criterion	Data available from cost-effectiveness analysis	Data available from CheckMate 141
The treatment is indicated for patients with a short life-expectancy, *normally* less than 24 months	Mean OS predicted in the base-case of the cost-effectiveness analysis was 8.4 months for IC. A mean OS of less than 24 months for the IC arm was predicted for all parametric survival distributions that were explored.	Median OS from CheckMate 141 for the IC arm was 5.1 months.
There is sufficient evidence to indicate that the treatment offers an extension to life, *normally* of at least an additional 3 months, compared with current NHS treatment	Mean OS predicted in the base-case of the cost-effectiveness analysis was 17.7 months for nivolumab, representing an extension in mean OS of 9.3 months relative to IC of therapy. An extension in OS of more than 3 months was predicted for each parametric survival distribution that was explored.	Median OS extended by 2.43 months in the nivolumab arm from CheckMate 141 trial
IC = investigator's choice; OS = overall survival		

Both criterion met although considerable uncertainty surrounding the results reported in the CheckMate 141 trial and its applicability in a UK setting.

Innovation

- Nivolumab has the potential to help address the considerable unmet medical need for these patients who currently have limited treatment options available to them at an end-of-life stage
  - For patients with R/M SCCHN who have progressed after platinum-based therapy there are no treatment options currently available which confer proven survival benefits in this patient population
  - Aim of current treatment for these patients, in the absence of effective, life-extending therapies, is therefore palliative.
- Introduction of nivolumab as a PD-1 immune-checkpoint inhibitor and well-tolerated therapy with demonstrable survival benefits represents a step-change in the management of platinum-refractory R/M SCCHN in the UK
- Awarded Breakthrough Therapy Designation and PIM designation by the FDA and MHRA respectively,

Key Issues (1)

- What are the committee's view on the relevance of CheckMate 141 to UK clinical practice?
  - Validity of comparison of nivolumab with IC which includes cetuximab (comparator not specified in NICE scope)
  - Male to female ratio in the trial
  - Differences in OS HR's between participants from North America and the European Union
- What are the committee's view of the robustness of trial results given the limitations?
- Does the committee accept the assumption of equivalence between the 3 comparators specified in NICE scope?
  - Docetaxel equivalent to paclitaxel
  - Docetaxel equivalent to methotrexate
- Does the committee accept the ERG base revisions as appropriate?
  - Distribution for extrapolating TTD in the model
  - Overall utility estimates rather than treatment-specific estimates
  - Docetaxel dose to reflect UK clinical practice
  - Treatment independent proportions for subsequent treatments
  - Incorporating pneumonitis as an AE

Key Issues (2)

- What are the committee's views on the appropriateness of the analyses carried out by the ERG?
  - Threshold analysis based on the assumption of equivalence between docetaxel and paclitaxel?
  - Shorter time horizons explored by the company and ERG
- What are the committee's views on other modelling assumptions?
  - Incorporating adverse events only once in the first cycle
  - FDA-updated nivolumab dose for other indications
- What are the committee's views on the plausibility of the post-progression benefits predicted by the model?
- Does the committee accept that the end of life criteria has been met for nivolumab in treatment of R/M SCCHN?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab within its marketing authorisation for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy.

Background

Head and neck cancer is a heterogeneous group of malignant tumours that arise in the head and neck at the following sites: skin and lip, oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, salivary glands, nasal cavity and paranasal sinuses, and external auditory meatus and middle ear. The most common histological type of head and neck cancer is squamous cell carcinoma (approximately 90%),[1] particularly that affecting the oral cavity, oropharynx and larynx. Although local metastases of head and neck cancer occur frequently (usually spreading through the lymphatic system in the neck), distant metastases are less common.

The annual incidence of head and neck cancer is estimated to be 0.022% and 0.009% for males and females, respectively, equating to approximately 8,000 cases in England each year.[2] Approximately 60% of patients present with locally advanced disease at diagnosis, and most of these develop local or regional recurrence, with approximately 20–30% developing distant metastases.[3] Survival depends on several factors, mainly the origin of the cancer and the stage of the disease at diagnosis. In 2012, there were 3,300 deaths in the UK.[4]

Treatment options for squamous head and neck cancer vary according to the specific sites involved. In some people with recurrent disease, the tumour may be amenable to surgery or radiotherapy with curative intent. In people with metastatic disease or who have previously received radiotherapy, palliative chemotherapy is normally given to control the disease and improve quality of life. Platinum-based chemotherapy is commonly used for recurrent or metastatic head and neck cancer. There is no established pathway of care when platinum-based therapy is not clinically appropriate.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a humanised monoclonal antibody that targets and blocks a receptor on the surface of lymphocytes known as PD-1. This receptor is part of the immune checkpoint pathway, and

blocking its activity may promote an anti-tumour immune response. Nivolumab is administered by IV infusion.

Nivolumab does not currently have a marketing authorisation in the UK for treating squamous-cell carcinoma of the head and neck after platinum-based therapy. It has been studied in a randomised controlled trial compared with investigator's choice of therapy of cetuximab, methotrexate or docetaxel in people with recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck.

Intervention(s)	Nivolumab
Population(s)	Adults with recurrent or metastatic squamous-cell carcinoma of the head and neck who have previously received platinum-based chemotherapy
Comparators	• docetaxel • paclitaxel • methotrexate
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	Related Guidelines: 'Cancer of the upper aerodigestive tract: assessment

and NICE Pathways	and management in people aged 16 and over'. Published February 2016. Related Quality Standards: 'Head and neck cancer'. NICE quality standard in development. Publication date February 2017. Related NICE Pathways: Head and neck cancer NICE pathway
Related National Policy	**NHS England** NHS England (2014) Manual for prescribed specialised services 13/14. Specialist cancer services (adults) 105 (page 235) NHS England. National Programmes of care and clinical reference groups. B16. Complex Head & Neck (accessed 14 10 2015) **National Service Frameworks** Cancer **Other policies** Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 2, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy

Final matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Bristol-Myers Squibb (nivolumab) Patient/carer groups • Black Health Agency • Cancer Black Care • Cancer Equality • Cancer Laryngectomee Trust • Cancer52 • Changing Faces • Get-A-Head • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Let's Face it • Macmillan Cancer Support • Maggie's Centres • Marie Curie • Mouth Cancer Foundation • Muslim Council of Britain • National Association of Laryngectomee Clubs • Oracle Cancer Trust • Rarer Cancers Foundation • Specialised Healthcare Alliance • South Asian Health Foundation • Swallows Head & Neck Cancer Support Group • Tenovus Cancer Care • The Royal Marsden Cancer Charity Professional groups • Association of Cancer Physicians • British Association of Head and Neck	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association for Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Accord Healthcare (docetaxel, methotrexate) • Actavis UK (docetaxel) • Dr. Reddy's Laboratories (docetaxel) • Hospira UK (docetaxel, methotrexate) • Medac GmbH (docetaxel) • Pfizer (methotrexate) • Sanofi (docetaxel) • Teva UK (docetaxel) Relevant research groups • Cochrane Ear, Nose and Throat Disorders Group • The Head and Neck Cancer Foundation • Institute of Cancer Research

Consultees	**Commentators (no right to submit or appeal)**
Oncologists • British Association of Head and Neck Oncology Nurses • British Association of Oral and Maxillofacial Surgeons • British Association of Otorhinolaryngologists • British Dietetic Association- Oncology Specialist Group • British Dental Health Foundation • British Geriatrics Society • British Institute of Radiology • British Oculoplastic Surgery Society • British Psychosocial Oncology Society • British Skull Base Society • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Bristol CCG • NHS Gloucestershire CCG • Welsh Government	• MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Saving Faces <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that manufactures the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that manufactures the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy

[ID971]

Company evidence submission

Bristol-Myers Squibb Pharmaceuticals Ltd.

August 2016

File name	Version	Contains confidential information	Date
ID971 BMS Nivolumab SCCHN final STA submission (redacted)	**1.1**	**Yes~~/no~~**	**28th October 2016**

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List of Abbreviations

Ab	antibody
AEs	adverse events
AHNS	American Head and Neck Society
AIC	Akaike Information Criterion
AIDS	acquired immunodeficiency syndrome
AMCP	Academy of Managed Care Pharmacy
ANCOVA	Analysis of Covariance Analysis
ASCO (QoC)	American Society of Clinical Oncology (Quality Care Symposium)
AST/ALT	aspartate aminotransferase/ alanine aminotransferase
BAHNO	British Association of Head and Neck Oncologists
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	best overall response
BSA	body surface area
CD28	cluster of differentiation 28
CHMP	Committee for Medicinal Products for Human Use
CI	confidence intervals
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CrCl	creatinine clearance
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
CT	computerised tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DALY	Disability Adjusted Life Years
DMC	Data Monitoring Committee
DOR	duration of response
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EHNS	European Head and Neck Society
EMA	European Medicines Agency
eMIT	electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire – Core 30
EORTC QLQ-H&N35	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire – Head and Neck 35
EQ-5D-3L	3-level EuroQoL 5-Dimensions
ESMO	European Society of Medical Oncologists
ESTRO	European Society for Radiotherapy and Oncology

FDA	Food and Drug Administration
GP	general practitioner
HBV sAg	hepatitis B virus surface antigen
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV-p16	human papillomavirus viral protein 16
HR	hazard ratio
HRG	Health Resource Group
HRQoL	health-related quality of life
HTAD	Health Technology Assessment Database
i.v.	intravenous
IC	investigator's choice
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IFNγ	interferon gamma
IFNγR	interferon gamma receptor
IgG4	immunoglobulin G4
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention to treat
IVRS	interactive voice response system
LYG	life-years gained
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
N/A	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NF-κB	nuclear transcription factor-κB
NHS	National Health Service
NHS EED	National Health Service Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
OCIU	Oxford Cancer Intelligence Unit
ONS	Office for National Statistics
OS	overall survival
PAS	Patient Access Scheme
PbR	Payment by Results
PD	progressed disease

PD-1	programmed death 1
PD-L1 and PD-L1	programmed death ligand 1 and 2
PF	progression free
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PIM	Promising Innovative Medicines
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROs	patient-reported outcomes
PSS	Personal Social Services
QALY	quality-adjusted life year
QW, Q2W and Q3W	once every week, once every two weeks and once every three weeks
R/M	recurrent or metastatic
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
SAEs	serious adverse events
SCC	squamous-cell carcinoma
SCCHN	squamous-cell carcinoma of the head and neck
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Result
Shp-2	Src homology 2 domain-containing protein tyrosine phosphatase 2
SLR	systematic literature review
SmPC	Summary of Product Characteristics
TTD	time to discontinuation
TTR	time to response
ULN	upper limit of normal
VAS	visual analogue scale
VAT	value-added tax
WBC	white blood cell
WOCBP	women of childbearing potential

1 Executive summary

1.1 Statement of decision problem

The objective of this appraisal is to determine the clinical and cost-effectiveness of nivolumab within its anticipated marketing authorisation for treating recurrent or metastatic (R/M) squamous-cell carcinoma of the head and neck (SCCHN) after platinum-based therapy.[1] Further details of the decision problem and how it has been addressed in this submission are presented in the table on page 13.

Platinum-refractory R/M SCCHN represents a condition for which there is a considerable unmet medical need – patients have limited treatment options and a short life-expectancy

Head and neck cancer is a broad term for cancers arising from several anatomical locations within the head and neck region, with the majority of tumours having squamous cell histology.[2, 3] Patients with SCCHN are likely to receive platinum-based therapy either at the locally advanced stage or for metastatic disease.[4, 5] For patients who progress after platinum-based therapy there are no currently-available therapies that offer a proven survival benefit, with the aim of existing therapies being palliative in nature only.[3, 6] In the absence of effective treatment options, these patients currently face an extremely poor prognosis with an estimated life-expectancy of less than 6 months.[7] Furthermore, with cytotoxic chemotherapy being the most routinely-used treatment approach, platinum-refractory R/M SCCHN patients treated with currently-available therapies may experience deterioration in health-related quality of life (HRQoL) due to drug-related adverse events (AEs) in addition to the impact of worsening disease symptoms.[8, 9]

New treatment approaches that offer patients convincing survival benefits, are well tolerated, and maintain HRQoL, are therefore urgently needed to address the unmet medical need for patients with R/M SCCHN who have progressed after platinum-based therapy.

1.2 Description of the technology being appraised

As an immune-checkpoint inhibitor that targets the programmed death 1 (PD-1) receptor, nivolumab harnesses the body's own immune system to destroy cancer cells and thus represents an entirely novel and highly innovative mechanism of action compared to currently-available therapies for this condition (see Section 2.1). Nivolumab is expected to be the first PD-1 inhibitor (or immune-checkpoint inhibitor) to receive a marketing authorisation in Europe for the treatment of SCCHN and has been awarded the Promising Innovative Medicines (PIM) designation by the Medicines and Healthcare products Regulatory Agency (MHRA) in recognition of the innovation that nivolumab represents as a treatment for adults with R/M SCCHN.

Given the novel mechanism of action by which nivolumab acts and the significant survival benefits seen in platinum-refractory R/M SCCHN patients treated with nivolumab in a phase III randomised controlled trial (RCT),[8, 9] nivolumab represents a step-change in the management of platinum-refractory R/M SCCHN in the UK, a condition for which there is a considerable unmet medical need. Long-term survival benefits with nivolumab have been demonstrated in the various other cancer indications in which its use has been investigated and for which data from longer follow-up are available, including advanced non-small cell lung cancer (NSCLC), advanced renal cell carcinoma (aRCC) and advanced melanoma.[10-12]

A summary of nivolumab is presented in Table 1.

Table 1: The technology being appraised

UK approved name and brand name	Nivolumab (Opdivo®)
Anticipated marketing authorisation	An application for a marketing authorisation in Europe for the indication detailed in this submission was submitted to the EMA on [redacted] and a positive opinion from the CHMP is anticipated on [redacted].
Indications and any restriction(s) as described in the SmPC	The anticipated indication for nivolumab as a treatment for SCCHN is detailed below: *"Nivolumab (Opdivo®) is indicated for the treatment of recurrent or metastatic squamous-cell cancer of the head and neck after platinum-based therapy in adults."* Nivolumab is also indicated as a treatment for the following: • As monotherapy, or in combination with ipilimumab, for the treatment of advanced (unresectable or metastatic) melanoma in adults • For the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults • As monotherapy for the treatment of advanced renal cell carcinoma after prior therapy in adults
Method of administration and dosage	Intravenous; 3 mg/kg Q2W, continued as long as clinical benefit is observed or until treatment is no longer tolerated

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; NSCLC: non-small cell lung cancer; Q2W: once every 2 weeks; SCCHN: squamous-cell carcinoma of the head and neck; SmPC: Summary of Product Characteristics.
Source: Nivolumab SmPC[13]

Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with R/M SCCHN who have previously received platinum-based chemotherapy.	Adults with R/M SCCHN who have previously received platinum-based chemotherapy.	N/A – the decision problem matches the final scope
Intervention	Nivolumab	Nivolumab	N/A – the decision problem matches the final scope
Comparator(s)	• Docetaxel • Paclitaxel • Methotrexate	• Docetaxel • Paclitaxel • Methotrexate	N/A – the decision problem matches the final scope
Outcomes	• Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	N/A – the decision problem matches the final scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	The economic analysis is consistent with the final scope, presenting results in terms of incremental cost per QALY and using an appropriate time horizon of 20 years. The perspective of the analysis was that of the NHS and PSS.	N/A – the decision problem matches the final scope
Subgroups to be considered	None detailed	N/A	N/A
Special considerations including issues related to equity or equality	None detailed	N/A	N/A

Abbreviations: IC: investigator's choice; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PSS: Personal Social Services; QALY: quality-adjusted life year; R/M: recurrent or metastatic; SCCHN: squamous-cell carcinoma of the head and neck.

Source: NICE final scope [ID971] – issue date: June 2016[1]

1.3 Summary of the clinical effectiveness analysis

In the CheckMate 141 phase III RCT, nivolumab demonstrated a favourable clinical profile compared to currently-available therapies, including:

- **Significant improvements in overall survival (OS) versus investigator's choice of therapy (docetaxel, methotrexate or cetuximab)**
- **Clinical benefits compared to IC of therapy in terms of tumour responses and maintenance of HRQoL**
- **A more favourable safety/tolerability profile compared to IC of therapy**

The clinical effectiveness and tolerability of nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy has been demonstrated in the pivotal phase III RCT, CheckMate 141 (see Section 4.3.1). In this global trial, nivolumab (n=240) was compared against a control arm of investigator's choice (IC) of therapy (n=121), which consisted of either docetaxel, methotrexate or cetuximab.[8, 9] The majority of patients in the IC arm who received at least one dose of study treatment (n=111), received either docetaxel (n=52; 47%) or methotrexate (n=46; 41%), with few patients receiving cetuximab (n=13; 12%).[8] IC of therapy was chosen as a comparator in this trial to reflect the lack of a single, universally-accepted therapy for the treatment of R/M SCCHN when considering global treatment practices (see Section 3.2). Docetaxel, methotrexate and cetuximab, specifically, were included as therapies in the IC arm for consistency with regional treatment guidelines for SCCHN, including the UK.[3, 14 15]

A clinical systematic literature review (SLR) identified no randomised trials, other than CheckMate 141, that investigated the use of comparators included in this appraisal versus one another or versus nivolumab as treatments for patients with platinum-refractory R/M SCCHN, specifically (see Section 4.1). Indirect comparisons between comparators included in this appraisal (and versus nivolumab) were therefore not considered possible due to insufficient clinical trial data. According to expert clinician feedback, however, the comparators included in the IC arm can be considered to be equivalent to one another in terms of OS.[6] Paclitaxel, another taxane that is included in the final scope for this appraisal, is also considered by clinicians to have similar OS to the therapies included in the IC arm.[7] Intention-to-treat (ITT) data from the IC arm of CheckMate 141 therefore represents estimates, most relevant to UK practice, of the treatment effect for each of the comparators included in this appraisal versus nivolumab for the patient population of interest.

The principal findings from the CheckMate 141 trial supporting the use of nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy are summarised below.

Nivolumab demonstrated significant improvements in OS versus IC of therapy; based on data from the IC arm, patients with platinum-refractory R/M SCCHN have a life expectancy of less than 6 months

- CheckMate 141 was designed such that a total of 278 deaths were required to test the hypothesis that the hazard ratio (HR) for death for nivolumab versus IC was 0.6667 (at 90% power using a 2-sided test and α=0.05 level), with one interim look planned after 195 (70%) deaths had occurred[8]
- CheckMate 141 was stopped early after 218 (78%) deaths had occurred on the recommendation of the independent Data Monitoring Committee (DMC). The interim analysis showed that the study had met the primary endpoint with nivolumab demonstrating significant improvements in OS relative to the IC arm (HR, 0.70 [97.73% confidence intervals (CI), 0.51 to 0.96; p=0.0101]), corresponding to a 30% reduction in the risk of death with nivolumab versus IC of therapy (see Section 4.7.1 for Kaplan-Meier curve).[8, 9]
- Median OS was prolonged in the nivolumab arm (7.5 months; 95% CI, 5.5 to 9.1) compared to IC (5.1 months; 95% CI, 4.0 to 6.0)[8, 9]
    - A higher proportion of patients in the nivolumab arm were alive and in follow-up after 12 months, with 1-year survival rates more than doubled for nivolumab (36.0%) compared to IC of therapy (16.6%)[8, 9]
    - Increasing evidence suggests that immune-checkpoint inhibitors (including those targeting PD-1 and cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) are characterised by survival curves with a long, plateauing tail for a subset of patients, and that marked differences in the shape of survival curves (OS and PFS) may be observed compared to standard cytotoxic therapies due to differences in mechanism of action.[16] Based on survival patterns observed in longer-term data for nivolumab in other cancer indications, and short-term follow-up from CheckMate 141, nivolumab may offer some patients a long-term, durable survival benefit due to its highly innovative mechanism of action as an immune-checkpoint inhibitor (see Section 2.5)[10, 12]
- In subgroup analyses of CheckMate 141, nivolumab demonstrated reductions in the hazard rate of death versus IC of therapy, regardless of human papillomavirus viral protein 16 (HPV-p16) status (positive or negative), programmed death ligand-1 (PD-L1) expression (≥1% or <1%), and selected baseline characteristics, including intended therapy for the IC arm (see Section 4.8)
- Nivolumab should be considered as a treatment for patients at an 'end-of-life' stage according to the National Institute for Health and Care Excellence (NICE) criteria:[17]
    - Patients with R/M SCCHN who have progressed after platinum therapy currently face a very poor prognosis, with life-expectancy on currently-available therapies of less than 6 months based on expert clinician feedback and median OS from the IC arm of CheckMate 141 (see Section 4.13.2)[6, 8, 9]
    - The absolute median OS benefit for nivolumab versus IC of therapy at the interim analysis was 2.4 months; this is clinically relevant given the low life-expectancy of patients with currently-available therapies, corresponding to a relative benefit of nivolumab versus IC of 1.47-fold[6, 8, 9]
    - Given that some patients may achieve long-term survival with nivolumab, the median value for OS does not necessarily represent the durable survival benefit that could

potentially be achieved by some patients.[18] The mean OS benefit with nivolumab was predicted to be greater than 3 months compared to the IC arm using extrapolated data from CheckMate 141 in the economic model, regardless of the parametric survival distribution used (see Table 27 in Section 5.3.2). In the base case analysis, mean OS predicted by the model was 17.7 months with nivolumab versus 8.4 months with IC of therapy, representing an extension in life of 9.3 months. Nivolumab should therefore be considered to offer an extension to life of greater than the 3 months that are *normally* required to meet the NICE end of life criteria

Nivolumab demonstrated further clinical benefits in terms of improved tumour response and the maintenance of HRQoL versus IC of therapy in CheckMate 141, and was also associated with a more favourable safety/tolerability

- The objective response rate (ORR) was more than doubled in the nivolumab arm (13.3%; 95% CI, 9.3, 18.3) compared to the IC arm (5.8%; 95% CI, 2.4, 11.6) (see Section 4.7.2)[9]
    - Furthermore, six patients in the nivolumab arm (2.5%) achieved a complete response, compared to only one patient in the IC arm (0.8%)
- Although median progression-free survival (PFS) was similar between nivolumab and IC study arms (2.0 months with nivolumab versus 2.3 months with IC), a delayed separation of Kaplan-Meier curves, characteristic of PFS patterns seen with nivolumab in other indications,[19, 20] in favour of nivolumab was observed (HR, 0.89; 95% CI, 0.70, 1.1; p=0.3236) (see Section 4.7.2)[9]
    - The proportion of patients still in follow-up who had not progressed or died at 6 months was more than doubled in the nivolumab arm (19.7%; 95% CI, 14.6, 25.4) compared to the IC arm (9.9%; 95% CI, 5.0, 16.9)[9]
- Given the late stage of disease, palliation of symptoms is a key aim of treatment with current therapies for patients with R/M SCCHN.[3, 15] In CheckMate 141, patient-reported outcomes were evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and head-and-neck-specific module (QLQ-H&N35),[9] with clinically meaningful changes defined as a change from baseline of ≥10 points.[9, 21] Health problems and perceived health status were also assessed using the 3-level version of the EuroQoL 5-Dimensions questionnaire (EQ-5D-3L).[14]
- Significant differences between treatment arms were observed in favour of nivolumab compared to IC of therapy ($p<0.05$) for multiple domains assessed using EORTC QLQ-C30 (e.g. physical functioning, role functioning, social functioning, fatigue, dyspnoea and appetite loss) and QLQ-H&N35 (e.g. pain and sensory problems)[22]
- Furthermore, HRQoL tended to remain stable for patients treated with nivolumab whereas IC of therapy led to meaningful declines in functioning and worsening of symptoms:
    - Patients in the IC arm reported meaningful worsening in scores for numerous scales of the EORTC QLQ-C30 (e.g. physical, emotional, and social functioning; fatigue; dyspnoea) and QLQ-H&N35 (e.g. pain, sensory problems, trouble with social contact, sticky saliva, nutritional supplement use). In contrast HRQoL in the nivolumab arm was generally stable with patients exhibiting no meaningful changes across the majority of EORTC QLQ-C30 and QLQ-H&N35 scales in the first 21 weeks of follow-up (see Section 4.7.2)[14]

    - Health problems, as measured by the EQ-5D-3L, were more prevalent in the IC arm than the nivolumab arm at various time points over the first 21 weeks of follow-up (see Section 4.7.2)[14]

- Nivolumab was generally well tolerated by patients in CheckMate 141 and was associated with a more favourable safety/tolerability profile compared to IC of therapy
    - The proportion of patients experiencing a drug-related Grade 3-4 AE or serious AE (SAE) in the nivolumab arm was less than half that reported in the IC arm (drug-related, Grade 3-4 AEs: 13.1% nivolumab versus 35.1% IC of therapy; drug-related, Grade 3-4 SAEs: 4.7% nivolumab versus 10.8% IC of therapy)
    - A lower proportion of patients discontinued treatment in the nivolumab arm versus the IC arm due to drug-related AEs of any grade (3.8% nivolumab versus 9.9% IC of therapy) (see Section 4.12).[9, 14]
    - 'Select' AEs (defined as AEs with a potential immunological cause that are of special clinical interest with the use of nivolumab) did occur, but were mostly Grade 1-2 and were generally manageable using the recommended treatment guidelines (see Section 4.12)[14]
    - No new safety concerns with nivolumab were identified in CheckMate 141, with a similar safety/tolerability profile observed to that seen in trials of nivolumab monotherapy in other cancer types (see Section 4.12)[13, 14]
    - An improved safety profile for nivolumab versus IC would be expected to translate into lower resource use requirements in treating AEs, as well as the improvements in HRQoL observed in the trial

1.4 Summary of the cost-effectiveness analysis

Methods of the cost-effectiveness analysis

A *de novo* cost-utility analysis was conducted to evaluate the incremental costs and health benefits of nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy versus each of the comparators for this appraisal (docetaxel, paclitaxel and methotrexate). As per previous oncology models submitted to NICE for nivolumab (and in appraisals of other therapies for R/M SCCHN), the analysis was undertaken using the partitioned survival approach to determine the proportion of patients in each cohort occupying each of the three health states included in the model: *progression free, progressed disease* and *death* (see Section 5.2)[19, 20, 23]

Clinical parameters used in the model (e.g. OS and PFS) were based on ITT data from the treatment arms of the CheckMate 141 trial (i.e. nivolumab and IC; see Section 5.3), that were extrapolated using appropriate survival analyses.[24] Extrapolated time to discontinuation (TTD) data from CheckMate 141 were also used to provide an accurate estimate of duration of therapy in the model and to account for the possibility that some patients may continue to receive treatment with nivolumab beyond disease progression (see Section 5.2.4)[i]. Treatment with nivolumab beyond progression was permitted in CheckMate 141 due to the possibility that some patients may experience an unconventional immune-related response (see Section 2.1), as is characteristic of immune-checkpoint inhibitors. Treatment-dependent health state utilities for the progression-free and progressed disease states were derived from the EQ-5D-3L data collected from patients in CheckMate 141. Additional inputs included in the model were based on information from CheckMate 141, previous technology appraisals and published sources identified in a SLR (see Section 5.4 for utilities and Section 5.5 for costs), and were validated by UK clinicians.[7] A Patient Access Scheme (PAS) representing a simple discount to the list price of [redacted] has been included in the economic analysis.

As recommended in the NICE reference case, a discount rate of 3.5% was applied to both costs and health benefits, measured in terms of quality-adjusted life-years (QALYs) gained.[25] The model perspective was that of the UK National Health Service (NHS) and Personal Social Services (PSS). In the base case analysis, the time horizon of 20 years (equivalent to 260× 4-week cycles) was chosen to ensure that all relevant costs and benefits were captured – at this point >99% of patients had died in the model.

Results of the cost-effectiveness analysis

The results of the base case deterministic analysis for nivolumab are provided in Table 3 (at PAS price). Nivolumab was associated with both increased costs and increased QALYs versus all three comparators. When provided with a PAS, nivolumab was associated with incremental cost-effectiveness ratios (ICERs) of between £34,777 and £34,908 per QALY versus the comparators listed in the scope; these ICERs were well below the cost-effectiveness threshold for therapies meeting the end-of-life criteria. Model results were tested in a range of scenario analyses exploring different modelling assumptions. These demonstrated the base case finding of cost-effectiveness of nivolumab when considered with the PAS to be robust to the vast majority of altered modelling assumptions (see Section 5.8).

[i] In CheckMate 141, patients otherwise stopped treatment on disease progression, unacceptable toxicity or withdrawal of consent

Table 3: Deterministic base case results (with PAS for nivolumab)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years

Concluding remarks

- Patients with R/M SCCHN who have progressed after platinum-based therapy are faced with a very poor prognosis and no treatment options that confer proven survival benefits and can maintain HRQoL
- These patients have an estimated life-expectancy of less than 6 months on currently-available treatments – these therapies are considered palliative only
- The introduction of nivolumab as the first immune-checkpoint inhibitor for this patient population represents an innovation, as recognised by the awarding of a PIM designation by the MHRA. Nivolumab is the first treatment to offer a proven survival benefit and thus represents a step-change in the management of platinum-refractory R/M SCCHN in the UK; a condition for which there is a considerable unmet medical need

- In the phase III RCT, CheckMate 141, nivolumab demonstrated significant improvements in OS versus the IC arm (docetaxel, methotrexate or cetuximab), corresponding to a 30% reduction in the risk of death with nivolumab versus IC of therapy (HR, 0.70; 97.73% CI, 0.51 to 0.96; p=0.0101)
  - 1-year survival rates were more than doubled in the nivolumab arm (36.0%) compared to IC of therapy (16.6%)
  - Long-term durable survival benefits with nivolumab have been demonstrated in other cancer indications for which data from longer follow-up are available
  - Modelled estimates of long-term OS for nivolumab as a treatment for platinum-refractory R/M SCCHN consistently predict a mean survival benefit of greater than 3 months with nivolumab versus IC of therapy under multiple different survival distributions
- Whereas treatment with IC of therapy was associated with meaningful declines in function and worsening of symptoms, nivolumab stabilised patient HRQoL in CheckMate 141, as assessed using PROs
- Nivolumab is generally well tolerated and demonstrated a more favourable safety/tolerability profile compared to IC of therapy in CheckMate 141

- Nivolumab is cost effective: when provided with a PAS, nivolumab is associated with ICERs of between £34,777 and £34,908 per QALY versus the comparators listed in the scope; these ICERs are well below the cost-effectiveness threshold for therapies meeting the end-of-life criteria and are robust to changes in the majority of modelling assumptions

2 The technology

2.1 Description of the technology

Brand name: Opdivo®

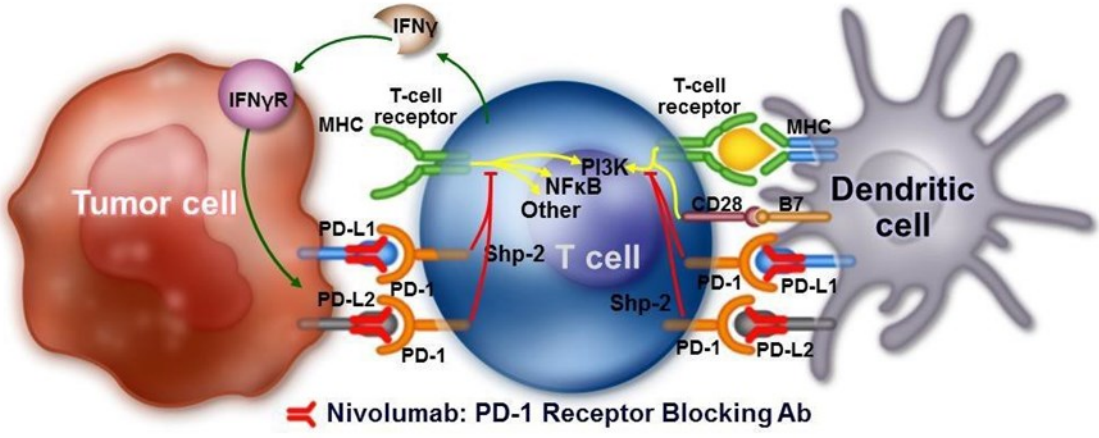
UK approved name: nivolumab

Therapeutic and pharmacological class: anti-neoplastic agent; monoclonal antibody

Brief overview of the mechanism of action:

A major part of the immune response to foreign antigens or cells is the activation of T-cells that can destroy them. Activation and de-activation of T-cells is regulated through a complex balance of positive and negative signals via receptors on the T-cell surface (see Figure 1). Cancer cells can exploit these pathways by stimulating inhibitory receptors and in doing so can avoid destruction and facilitate tumour development.[26] Antibodies designed to bind to and block these inhibitor receptors can prevent tumour-driven T-cell suppression and allow restoration of T-cell activity, as depicted in Figure 1.

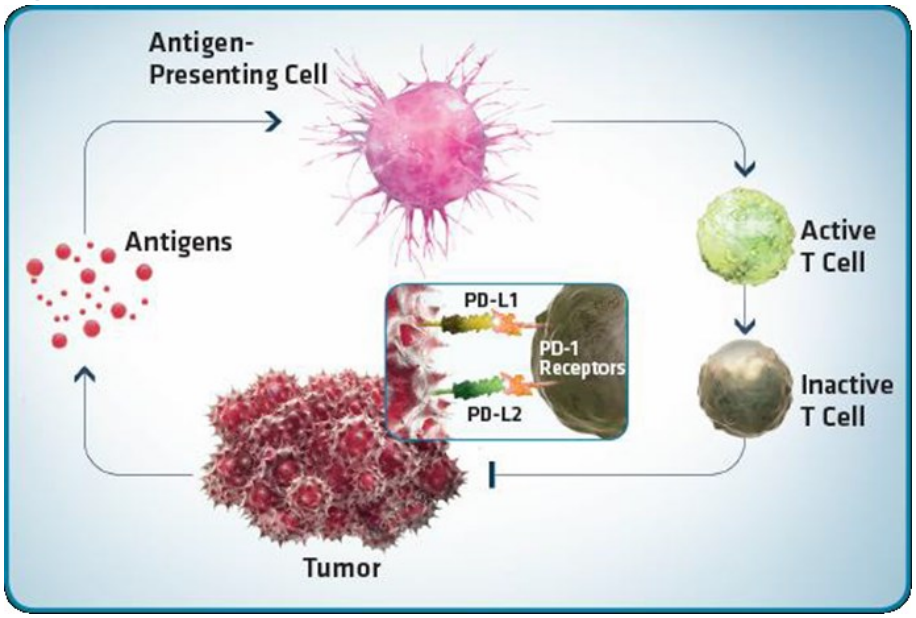
Figure 1: Regulation of the T-cell immune response



Abbreviations: Ab: antibody; CD28: cluster of differentiation 28; IFNγ: interferon gamma; IFNγR: interferon gamma receptor; MHC: major histocompatibility complex; NF-κB: nuclear transcription factor-κB; PD-1: programmed death 1; PD-L1: programmed death-ligand 1; PD-L2: programmed death-ligand 2; PI3K: phosphoinositide 3-kinase; Shp-2: Src homology 2 domain-containing protein tyrosine phosphatase 2.

The programmed death 1 (PD-1) receptor is a negative regulator of T-cell activity and is expressed on activated T-cells. Interaction of PD-1 with its ligands (programmed death-ligand 1, PD-L1, and programmed death-ligand 2, PD-L2) results in the inhibition of T-cell activation and subsequent T-cell death. PD-L1 and PD-L2 are expressed on antigen-presenting cells (such as dendritic cells), and may also be expressed by tumours or other cells in the tumour microenvironment (see Figure 2).[27, 28] There is increasing evidence that implicates the PD-1 signalling pathway in SCCHN tumour evasion,[29] thus providing compelling biological rationale for the blocking of PD-1 as a therapeutic target.

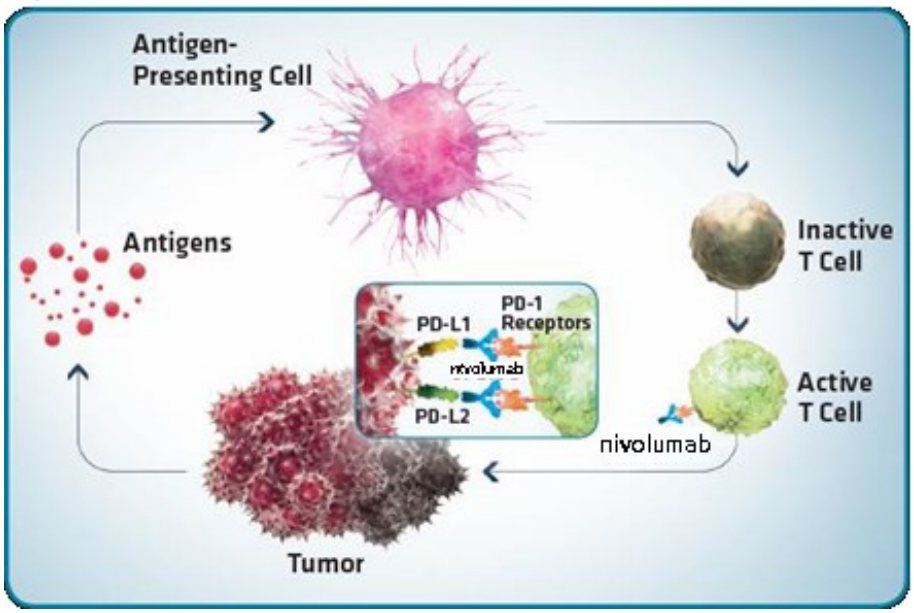
Figure 2: Tumour immune evasion



Abbreviations: PD-1 programmed death 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2.

Nivolumab (Opdivo®) is a human, monoclonal immunoglobulin G4 (IgG4) antibody that acts as a PD-1 inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2 (see Figure 3). As such, by preventing inactivation of T-cells, nivolumab effectively restores T-cell activity against tumour cells, i.e. nivolumab harnesses the patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" antigen), resulting in destruction of the tumour. Nivolumab is anticipated to be the first immune-checkpoint inhibitor or PD-1 inhibitor approved in Europe for R/M SCCHN.

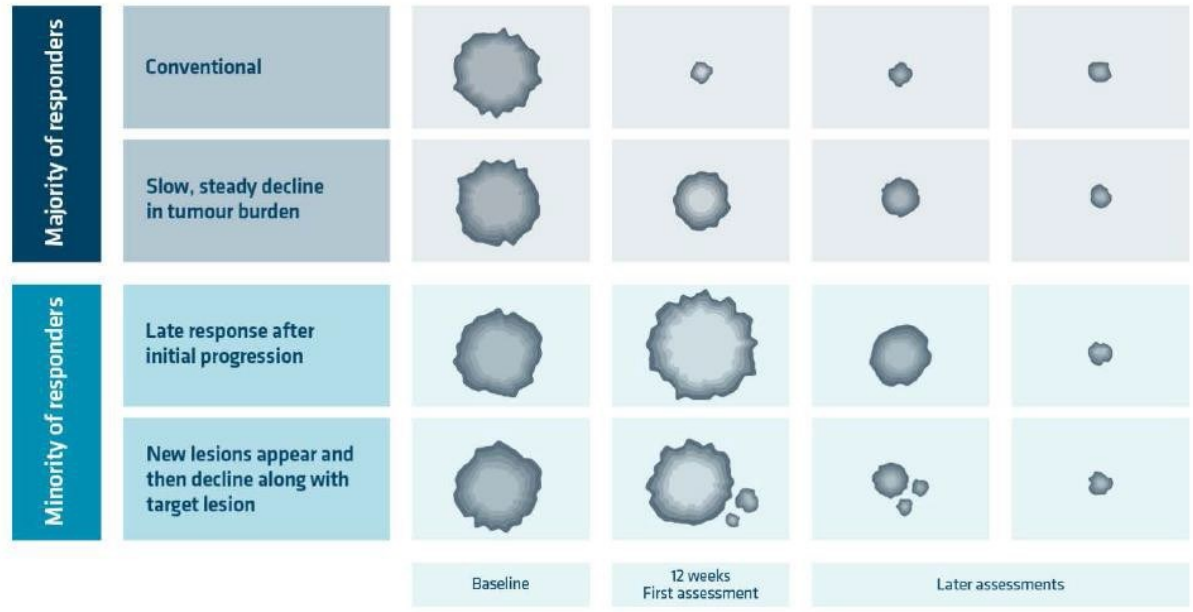
Figure 3: Nivolumab stimulation of immune-mediated destruction



Abbreviations: PD-1 programmed death 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2.

Contrary to conventional anti-cancer therapies, where response to treatment is observed as an immediate shrinkage of the tumour, immune-mediated tumour destruction results in varying patterns of response. In some cases, immune-checkpoint inhibitors can have an initial effect of making the tumour appear bigger and is thought to be due to the proliferation of activated T-cells infiltrating the tumour to destroy it. This is commonly referred to as an "unconventional immune-related response" and can result in "pseudo-progression," where patients who ultimately achieve a positive clinical outcome may appear to have tumours that appear to have enlarged when assessed in the early stages of treatment. Typical patterns of response observed with immunotherapies are presented in Figure 4.

Figure 4: Typical patterns of response observed with immune-checkpoint inhibitors



2.2 Marketing authorisation and health technology assessment

Marketing authorisations

The anticipated indication for nivolumab as a treatment for SCCHN is detailed below:

"Nivolumab (Opdivo®) is indicated for the treatment of recurrent or metastatic squamous-cell cancer of the head and neck after platinum-based therapy in adults."

An application for a marketing authorisation in this indication in Europe was submitted to the European Medicines Agency (EMA) on [redacted] and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is anticipated on [redacted]. The draft Summary of Product Characteristics (SmPC) for nivolumab, which details the anticipated licensed indication for nivolumab in SCCHN, is provided in the reference pack accompanying this submission.[13]

Nivolumab has also been filed for a marketing authorisation in the same SCCHN indication in the USA and has been granted Breakthrough Therapy Designation by the US Food and Drug Administration (FDA).[30] The Breakthrough Therapy Designation reflects the innovative nature and potential benefit of nivolumab to address an unmet medical need.[31] Similarly in the UK, the PIM designation has been awarded by the MHRA in recognition of innovative value of nivolumab as a treatment for adults with R/M SCCHN. [redacted]

[redacted].

Nivolumab has already been granted a marketing authorisation by the EMA for the following indications, as detailed in the SmPC:[13]

- As monotherapy or in combination with ipilimumab, for the treatment of advanced (unresectable or metastatic) melanoma in adults
- For the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults
- As monotherapy for the treatment of advanced renal cell carcinoma after prior therapy in adults

Nivolumab was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world in July 2014, and currently has regulatory approval in 54 countries including the United States, Japan, and in the European Union.[32]

Health Technology Assessment

Bristol-Myers Squibb Pharmaceuticals Ltd will submit nivolumab as a treatment for patients with R/M SCCHN after platinum-based therapy for health technology assessment with the Scottish Medicines Consortium (SMC) and the National Centre for Pharmacoeconomics in the Republic of Ireland.

Nivolumab has been appraised by NICE for the following indications:

- Nivolumab for treating advanced (unresectable or metastatic) melanoma [TA384, 2016] [*recommended*][33]
- Nivolumab in combination with ipilimumab for treating advanced melanoma [TA400, 2016] [*recommended*][34]

At the time of submission, NICE appraisal guidance is also in development for the following additional indications:

- Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer [ID811, expected publication date: to be confirmed][35]
- Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer [ID900, expected publication date: September 2016][36]
- Nivolumab for previously treated advanced or metastatic renal cell carcinoma [ID853, expected publication date: October 2016][37]

In addition, nivolumab has also been accepted for use in Scotland by the SMC for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults (SMC ID 1114/16),[38] and as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults (SMC ID 1120/16).[39]

2.3 Administration and costs of the technology

A summary of the costs and administration requirements associated with nivolumab is presented in Table 4. A PAS has been submitted to the Department of Health for inclusion in this technology appraisal. This PAS represents a simple discount on the list price, as detailed in Section 1.4.

Table 4: Costs of the technology being appraised

	Cost		Source
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate)		SmPC[13]
Acquisition cost (excluding VAT)	40 mg vial	100 mg vial	British National Formulary (2016)
	List price: £439.00	£1,097.00	
	PAS price: [redacted]	[redacted]	
Method of administration	Intravenous infusion, over 60-minutes		SmPC[13]
Doses	3 mg/kg		SmPC[13]
Dosing frequency	Every 2 weeks		SmPC[13]
Average length of a course of treatment	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient The mean duration of therapy with nivolumab predicted in the economic analysis was [redacted]. Duration of therapy was modelled based on time to discontinuation data from the pivotal phase III RCT, CheckMate 141.		SmPC[13] Section 5.3.4
Average cost of a course of treatment	Based on results of the economic analysis, the average cost of nivolumab is estimated to be: **List price:** [redacted] **PAS price:** [redacted]		British National Formulary (2016)
Anticipated average interval between courses of treatments	Retreatment is not anticipated		-
Anticipated number of repeat courses of treatments	Retreatment is not anticipated		-
Dose adjustments	Dose escalation or reduction is not recommended; dosing delay or discontinuation may be required based on individual safety and tolerability.		SmPC[13]
Anticipated care setting	In a hospital or clinic; to be initiated and supervised by a physician experienced in the treatment of cancer		SmPC[13]

Abbreviations: CI: confidence intervals; PAS: Patient Access Scheme; RCT: randomised controlled trial; SmPC: Summary of Product Characteristics; VAT: value-added tax.

2.4 Changes in service provision and management

As detailed in the SmPC, nivolumab treatment must be initiated and supervised by physicians experienced in the treatment of cancer.[13] Hospital oncology units already have the staffing and infrastructure needed for the administration of intravenous cancer treatments. Administration of nivolumab is therefore not expected to require any additional NHS infrastructure. It should be noted that each of the comparators included in the final scope for this appraisal are also intravenously administered (see Section 5.5.2).

There are however some differences in the frequency of administration of nivolumab relative to comparator therapies, with nivolumab (once every two weeks, Q2W) administered less frequently than methotrexate or paclitaxel (once every week, QW) – both of these comparator therapies are often used to treat patients who cannot tolerate docetaxel.[7] Docetaxel, which is most routinely used in UK clinical practice, may be administered less frequently than nivolumab (once every three weeks, Q3W), although the dosing of docetaxel used in the CheckMate 141 study was once every week (see Section 4.3.1). These differences in administration frequency, in addition to management of AEs (see Section 2.4.1), are the only expected source of differential resource use to the NHS for nivolumab relative to current clinical comparators.

2.4.1 Managing adverse events

Nivolumab is generally well tolerated by patients with R/M SCCHN, as detailed in Section 4.12. However, AEs observed with immunotherapies, such as nivolumab, may differ from those observed with non-immunotherapies. Early identification of AEs and intervention are an important part of the safe use of nivolumab. The immune-based mechanism of action of nivolumab means many of its treatment-related AEs are immunological in origin. Immune-related AEs associated with nivolumab, including severe AEs, are well characterised and are generally manageable with topical and/or systemic immunosuppressants.[13] They are often resolved following initiation of appropriate medical therapy or withdrawal of nivolumab.[13] A full list of AEs and guidelines for discontinuation or withholding of doses in response to immune-related AEs is provided in the SmPC.[13]

As detailed in the SmPC for nivolumab, adequate evaluation should be performed to confirm aetiology or exclude other causes for suspected immune-related AEs.[13] Based on the severity of the AE, nivolumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month's duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

Nivolumab should not be given while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

2.5 Innovation

For patients with R/M SCCHN who have progressed after platinum-based therapy there are no treatment options currently available which confer proven survival benefits in this patient population (see Sections 3.2 and 3.3). These patients have an estimated life-expectancy of less than 6 months on currently-available treatments and are thus considered to be at an end-of-life stage.[6] The aim of treatment for these patients, in the absence of effective, life-extending therapies, is therefore palliative.[3, 6] New treatment approaches that offer patients convincing survival benefit and maintain HRQoL are therefore urgently needed to address the unmet medical need for patients with R/M SCCHN who have progressed after platinum-based therapy.

Nivolumab is the first PD-1 immune-checkpoint inhibitor to demonstrate a survival benefit over currently-available therapies for the treatment of platinum-refractory R/M SCCHN. As detailed in Section 2.1, rather than relying on the indiscriminate cytotoxic effects of chemotherapy, nivolumab harnesses the body's own immune system to destroy cancer cells via the restoration of anti-tumour T-cell activity and thus represents a highly innovative mechanism of action. The awarding of a Breakthrough Therapy Designation and PIM designation by the FDA and MHRA, respectively, is recognition of the innovative nature of nivolumab.[30]

[redacted]

With this innovative mechanism of action, nivolumab has demonstrated improved overall survival versus single-agent chemotherapies currently used in UK clinical practice for the treatment of platinum-refractory R/M SCCHN, with 1-year survival rates more than doubled in the nivolumab arm of the CheckMate 141 trial (36.0%), relative to the comparator IC arm of docetaxel, methotrexate or cetuximab (16.6%) (see Section 4.7.1).[8, 9] Furthermore, long-term survival benefits with nivolumab have been observed in the other cancer indications that have been investigated, such as advanced NSCLC, aRCC and advanced melanoma, and for which data from longer follow-up are available.[10-12] The plateauing of the Kaplan-Meier curve at a higher proportion of patients with nivolumab versus IC of therapy in CheckMate 141 suggests that nivolumab may potentially offer some patients with platinum-refractory R/M SCCHN a considerable extension in life relative to current treatment approaches (see Section 4.7.1).

In addition, nivolumab was associated with a more favourable safety/tolerability profile compared to the IC arm of CheckMate 141 (see Section 4.12), with an almost three-fold decrease in drug-related grade 3-4 AEs in the nivolumab arm compared to IC (13.1% versus 35.1%), suggesting that nivolumab may offer improvements in tolerability compared to the cytotoxic chemotherapies that represent the currently-available therapies for these patients.

Summary of innovation

- The introduction of nivolumab as a highly-innovative and well-tolerated therapy with demonstrable survival benefits represents a step-change in the management of platinum-refractory R/M SCCHN in the UK
- Nivolumab has the potential to help address the considerable unmet medical need for these patients who currently have limited treatment options available to them at an end-of-life stage

3 Health condition and position of the technology in the treatment pathway

Summary of the health condition

- SCCHN comprises a group of malignancies that most commonly include tumours arising in the oral cavity, pharynx and larynx
- The prognosis for patients with R/M SCCHN who have progressed after platinum-based chemotherapy is extremely poor, with a life-expectancy of less than 6 months with currently-available therapies
  - Patients are considered to be at an end-of-life stage with limited treatment options for extending life
- Given the location of tumours and anatomical sites affected, SCCHN has substantial negative impacts on patient HRQoL, with detrimental effects to functional, social and psychological well-being
- The aim of treatment for patients with R/M SCCHN who have progressed after platinum-based therapy is currently often palliative; single-agent chemotherapies do not lead to significant improvements in HRQoL and are often associated with side-effects that impact negatively on HRQoL

Treatment pathway

- There is no single, universally-accepted therapy for patients with R/M SCCHN who have progressed after platinum-based chemotherapy
  - No treatments have been recommended to date by NICE in this indication
- Clinician preference would be to refer patients into a clinical trial given the limitations of currently-available therapies. Failing that, single-agent docetaxel is the most commonly-used therapy in current UK clinical practice, with paclitaxel (another taxane) and methotrexate also used but to a lesser extent than docetaxel
  - Choice of therapy is determined by the type of prior treatment received and patient fitness; based on expert clinician feedback, efficacy is believed to be similar between docetaxel, paclitaxel and methotrexate in terms of OS (limited direct evidence is available from randomised trials)
- Nivolumab is positioned in this submission as a treatment for adults with R/M SCCHN who have progressed after platinum-based chemotherapy in any setting, in line with the anticipated licence and patient population expected to be eligible to receive nivolumab in UK clinical practice

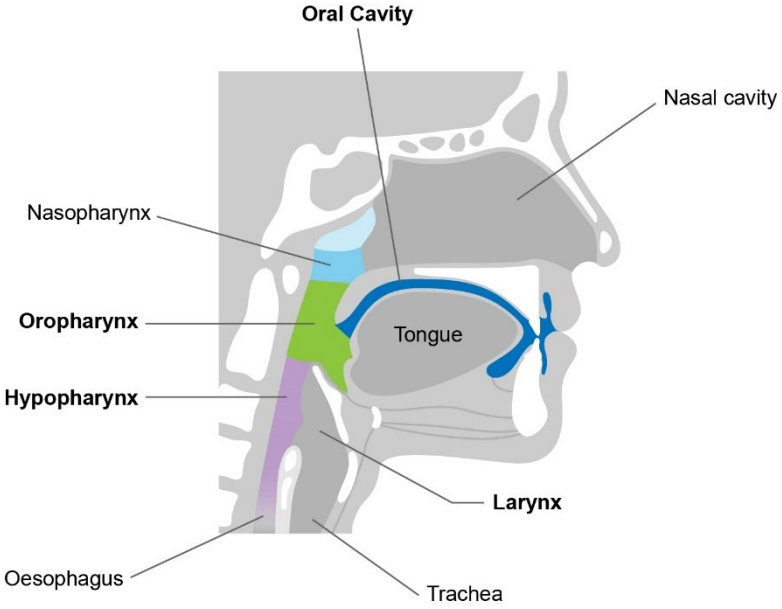
3.1 Disease background

Overview of head and neck cancer

Head and neck cancer is a broad term for cancers that arise from several anatomical locations within the head and neck region.[29] The term head and neck cancers excludes tumours of the brain and related tissues. The most common sites of tumours are those arising principally from the mouth (oral cavity), voice box (larynx) and the pharynx (consisting of the nasopharynx, oropharynx and hypopharynx) (see Figure 5).[30] Despite the wide variety of anatomical sites from which head and neck tumours arise, more than 90% of all malignant tumours in the head and neck are squamous cell carcinomas (SCC) arising from the lining mucosa.[3]

The survival outlook for patients varies between tumour sites; for example, cancers of the hypopharynx are associated with a less favourable prognosis.[40, 41] However, for patients with R/M SCCHN, the management of disease, as described in Section 3.2, is consistent across tumour sites.[15]

Figure 5: Anatomical locations within the head and neck region



Head and neck cancers can be further categorised by the stage of disease.[3] Tumours are staged by the UICC TNM Classification of Malignant Tumours, a system that describes the anatomical extent of disease based on an assessment of the extent of the primary tumour, the absence or presence and extent of regional lymph node metastasis, and the absence or presence of distant metastasis. The staging system describes the size of the tumour (T 1–4), whether the cancer cells have spread into the adjacent lymph nodes (N 0–3) and whether the cancer has metastasised (M 0–1). TNM stages are grouped according to prognosis and treatment into broader stage categories (numbered I–IV). Using the TNM staging system, metastatic disease is referred to as stage IVc (any T; any N; M1).[3]

The stage of disease at diagnosis has prognostic importance and is pivotal to informing and tailoring therapeutic decisions. The majority of patients with SCCHN present with advanced stage disease (approximately 60%), with up to 20–30% of patients going on to develop local and/or regional recurrences and distant metastases.[4] A small proportion of patients in the UK (around 4%) will present with metastatic disease.[42]

Patient prognosis is highly dependent on both the tumour site and the stage at diagnosis, with patients who are diagnosed and receiving treatment at an early stage having improved survival rates compared to those whose cancer is identified at (or has progressed to) a later stage of disease.[40, 41] For patients with platinum-sensitive R/M disease treated with platinum-based therapy, survival rates of 32.4%, 12.3% and 3.6% for 1-year, 2-year and 5-year survival, respectively, have been reported in one pooled analysis of two phase III RCTs.[43] The prognosis for patients whose cancer has progressed following platinum-based therapy is further reduced compared to those who are platinum-sensitive, as demonstrated by the low 1-year survival rate (16.6%) in the IC arm of the CheckMate 141 trial (see Section 4.7.1).[8] The life-expectancy of patients with R/M SCCHN who have progressed after platinum-based therapy is discussed further in Section 3.3.

Aetiology of disease and associated risk factors

In the UK, SCC of the oral cavity, pharynx and larynx typically affects more males than females (approximately 2.4:1) and peak incidence is typically between 60–70 years of age.[44] In the 2014 National Audit of Head and Neck Cancer (England and Wales), the mean age of patients at diagnosis was 63.9 years.[40] The major risk factors for SCCHN, in addition to age and gender, are tobacco and alcohol use, which account for as many of 75% of all cases worldwide.[2] The possible association of these risk factors with socioeconomic status may partially account for the geographical variation of SCCHN in the UK, with the north and west of England generally having a higher incidence of SCCHN.[40]

Viral infection is another recognised risk factor for head and neck cancer, with a link between infection with HPV and oropharyngeal cancer, in particular, having been established.[2] HPV-related oropharyngeal cancer typically occurs in younger patients (aged 40–50 years old) and these patients tend to have fewer comorbidities.[2] At present, however, the type of therapy used in the treatment of R/M SCCHN is not influenced by HPV status.[15] Expression of the p16 viral protein is used as a diagnostic measure of HPV-related oropharyngeal cancer and testing for p16-expression is currently recommended by NICE for all patients with SCC of the oropharynx [NG36, 2016].[45, 46] In the CheckMate 141 trial (see Section 4), the documentation of HPV-p16 status at baseline was required for all patients with oropharyngeal disease, and median OS by HPV-p16 status was assessed as part of subgroup analyses (see Section 4.8).

Impact of SCCHN on patients, carers and society

SCCHN has a highly detrimental impact on patient HRQoL, with patients experiencing significant impairments in functional, social and psychological well-being.[47, 48] Functional impairments can include increased pain, problems with eating and swallowing, dry mouth, and speech difficulties, while psychosocial changes can include heightened levels of anxiety and depressive symptoms, and reduced social interactions.[49] Early-stage interventions can also negatively impact HRQoL; for example, surgery can result in permanent physical changes in appearance and voice which may affect patients' emotional well-being and overall self-perception, and radiotherapy may have lasting impacts on swallowing, speech and taste.[50, 51]

Patient HRQoL has been shown to be associated with disease stage, with patients with late-stage SCCHN having worse HRQoL compared to those with earlier-stage disease.[52, 53] Given the poor prognosis of patients with R/M SCCHN, the aim of treatment with currently-available therapies is largely palliative rather than curative.[3, 15] Disease control and the maintenance of HRQoL are therefore important outcomes for R/M SCCHN patients who are otherwise at an end-of-life stage. For R/M SCCHN patients treated with platinum-based therapies in clinical trials,

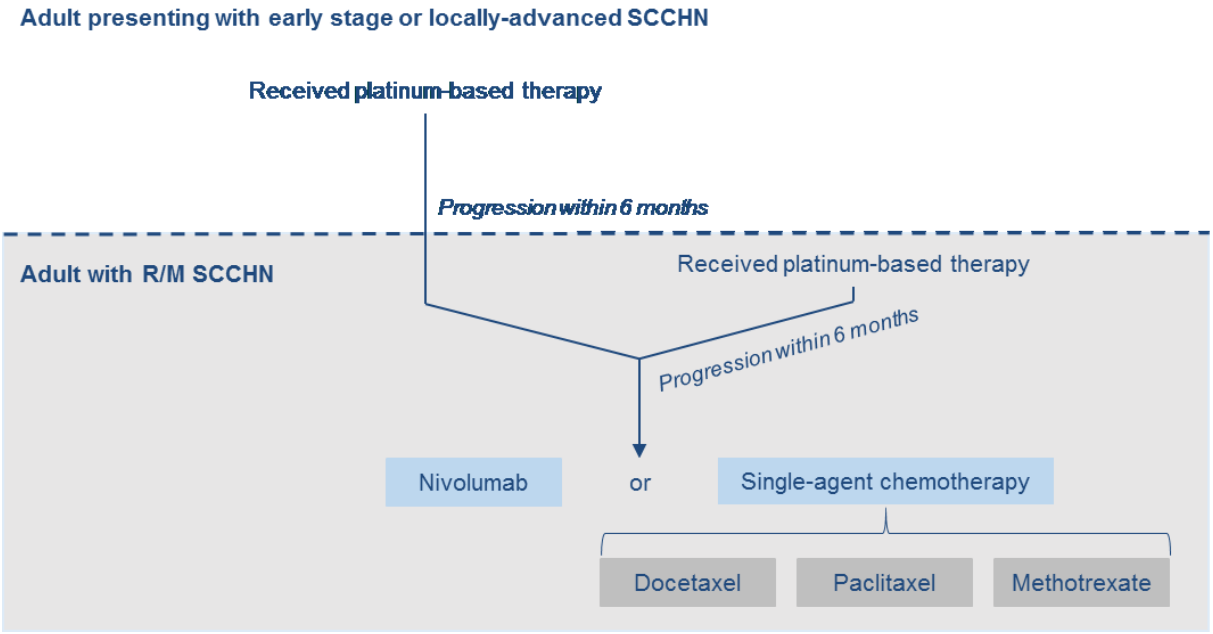
improvements in the severity of impairments, such as pain, swallowing and speech, have been reported; however, such improvements were not observed in trials with platinum-refractory patients treated with non-platinum single agents, such as methotrexate.[54] Furthermore, side-effects, such as diarrhoea, vomiting and dyspnoea, that are commonly associated with chemotherapies, including docetaxel, can have highly detrimental impacts on patient HRQoL.[55] For R/M patients who are refractory to platinum-based therapy, there is therefore an unmet medical need for effective treatments that can maintain levels of HRQoL.

In addition to the impact on the patient, SCCHN can also present a significant burden to informal caregivers, particularly in terms of emotional distress.[56] Moreover, for younger patients of working age, the detrimental impact of SCCHN is likely to affect work productivity and employment status.[57] The impact of treatment on these latter points are not captured in the QALY measure used for the calculation of health benefits in the cost-effectiveness analysis described in Section 5.

3.2 Clinical pathway of care

In this submission, nivolumab is considered as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy, as per the anticipated indication. The positioning of nivolumab with respect to the current clinical pathway of care is presented in Figure 6.

Figure 6: Clinical care pathway for adults with R/M SCCHN who have progressed after platinum-based therapy



Patients with SCCHN may receive platinum-based therapy in the R/M setting or as part of an earlier-stage intervention (e.g. with radiotherapy or in combination with other chemotherapy agents, such as cetuximab, for the treatment of locally advanced disease).[3]
Patients who may be considered eligible for treatment with nivolumab under the anticipated indication for SCCHN are expected to have progressed within 6 months of having received platinum-based therapy, but may have received this therapy in either setting.
Docetaxel is the most routinely-used agent in UK clinical practice for patients with R/M SCCHN who have progressed after platinum-based therapy.

Abbreviations: R/M: recurrent or metastatic; SCCHN; squamous-cell carcinoma of the head and neck.

Currently, there is no single, universally-accepted therapy for patients with R/M SCCHN who have progressed after platinum-based therapy. This is reflected in the lack of specific treatment recommendations for these patients in clinical guidelines from the British Association of Head and Neck Oncologists (BAHNO, 2011) and the European Head and Neck Society-European Society of Medical Oncologists-European Society for Radiotherapy and Oncology (EHNS-ESMO-ESTRO, 2010) Guidelines Working Group, both of which cite a lack of direct, comparative evidence between currently-available therapies in this setting.[3, 15] Furthermore, no therapies have been recommended by NICE for the treatment of patients with R/M SCCHN who have progressed after platinum-based therapy (see Section 3.4).

According to expert clinician feedback, enrolling into a clinical trial with an investigational therapy would be preferable for patients with R/M SCCHN who have progressed after platinum-based therapy.[7] Failing that, single-agent docetaxel is the most routinely-used treatment in current UK clinical practice.[7]. A medical chart review of patients in the UK with repeatedly-treated metastatic SCCHN (≥3 lines of therapy), found docetaxel, paclitaxel and cetuximab (second line); and docetaxel, methotrexate and cetuximab (third line) to be the most frequently used therapies in each of the respective lines of therapy for metastatic disease.[5] Platinum-based therapies were predominantly used in the first-line setting.[5] Docetaxel, paclitaxel and methotrexate are all included as comparators for nivolumab in the final scope for this appraisal (see Section 1.1).[1]

The choice of therapy is often determined by the type of prior therapies received and overall patient fitness.[6] For example, patients who have received prior treatment with a taxane will most likely receive methotrexate, as will patients with poor overall fitness and those who cannot tolerate docetaxel.[6] Although there are differences in the safety profiles between the taxanes (docetaxel and paclitaxel) and methotrexate, clinical expert opinion is that these treatments have similar efficacy in terms of OS.[6, 7] There is however limited direct evidence from clinical trials that assess the efficacy of these treatments against each other or against best supportive care, as noted in BAHNO 2011 guidelines.[15] In a phase II study (n=57) of docetaxel versus methotrexate, a significantly higher tumour response rate was observed in the docetaxel arm but OS and time to progression were considered superimposable between treatment groups.[58]

Clinical evidence for the safety and efficacy of nivolumab versus docetaxel and methotrexate is presented in this submission from the phase III RCT, CheckMate 141 (see Section 4), which included both of these therapies as part of the IC of therapy arm.[8, 9] Cetuximab (monotherapy) was also included in the IC arm of CheckMate 141 but this therapy is not believed to be routinely used in UK clinical practice, which is reflected in absence of this therapy as a comparator in the final scope.[1, 7, 8] The inclusion of cetuximab as part of the IC arm in the CheckMate 141 trial reflects the global nature of the trial and the lack of a single, universally-accepted therapy for the treatment of platinum-refractory R/M SCCHN when considering global treatment practices.[14] In total, only 12% of patients who received at least one dose of therapy in the IC arm received cetuximab.[8]

3.3 Life-expectancy, prevalence and incidence of the disease

Life-expectancy

In the CheckMate 141 trial, the 1-year survival rate in the IC arm (docetaxel, methotrexate or cetuximab) was 16.6%.[8] Compared to the 1-year survival rates of patients at their initial presentation with SCCHN in UK clinical practice (range, 76.0–90.4%, any stage; oral cavity, larynx, oropharynx or hypopharynx), the prognosis for patients with platinum-refractory R/M SCCHN, specifically, is very poor with currently-available therapies.[40]

According to expert clinician feedback, the current life-expectancy of patients with R/M SCCHN who have progressed after platinum-based therapy is estimated to be less than 6 months,[6] which is well below the 24 months considered by NICE to represent the end-of-life setting.[17] This is supported by with the median OS observed in the IC arm of CheckMate 141 (5.1 months; 95% CI, 4.0 to 6.0; see Section 4.7).[8, 9]

Population estimates

In 2014, 9,899 patients were newly diagnosed with head and neck cancer in England and Wales (see Table 5), with cancers of the oral cavity, larynx and pharynx representing the majority of reported cases (87%).[44, 59] In addition to the small proportion of patients who present with metastatic SCCHN (around 5%)[7, 42], as many as 30% of patients who present with earlier-stage SCCHN are expected to develop R/M disease.[4] Patients may be eligible for treatment with nivolumab if they have progressed after receiving platinum-based therapy (i.e. are platinum-refractory). Patients may have received platinum-based therapy for the treatment of locally advanced disease and then progressed to the R/M setting. Alternatively, they may have received platinum as a therapy in the R/M setting (see Section 3.2).

The number of patients in England and Wales eligible for treatment with nivolumab, as per the anticipated indication for SCCHN, is estimated to be 576 per year. Full details regarding the calculation for this eligible patient population are presented in Section 6.1.

Table 5: Newly diagnosed cases of head and neck cancer in England and Wales (2014)

Tumour site (ICD-10 code)	England	Wales	Total
Any site (ICD-10 C00 to C14, C30-C32)	9,257	642	9,899
Oral cavity (ICD-10 C00 to C06)	4,069	289	6,709
Pharynx (ICD-10 C09 to C14)[a]	2,351		
Larynx (ICD-10 C32)	1,822	119	1,941

[a] Only cases of oropharyngeal cancer (ICD-10 C10) are reported for Wales.
Individual C00–C97 codes refer to diseases classified as 'malignant neoplasms' by the World Health Organisation in the ICD-10.

Abbreviations: ICD: International Classification of Diseases.
Source: Office for National Statistics: cancer registrations, England (2014)[44] and Wales Cancer Intelligence and Surveillance Unit (2001-2014)[59]

3.4 Clinical guidance and guidelines

Relevant NICE guidance and guidelines

NICE clinical guidelines and published technology appraisals of relevance to this submission are listed below:

- NICE Cancer Services Guidance 6 [NCSG6, 2004]: Improving outcomes in head and neck cancers[60]
- NICE Guidelines 36 [NG36, 2016]: Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over[46]

No specific guidance has been issued by NICE for the treatment of patients with R/M SCCHN who have progressed after platinum-based therapy.

Relevant clinical guidelines

The latest treatment guidelines of relevance to this submission from the BAHNO and the EHNS-ESMO-ESTRO Guidelines Working Group are listed below:

- BAHNO: Head and Neck Cancer – Multidisciplinary management guidelines (September 2011)[15]
- EHNS-ESMO-ESTRO: Squamous-cell carcinoma of the head and neck: clinical practice guidelines for diagnosis, treatment and follow-up (May 2010)[3]

It should be noted that these guidelines, published in 2011 and 2010 respectively, may not fully represent current clinical practice in the UK and hence recent clinical expert opinion has also been used to inform considerations of the clinical pathway of care described in Section 3.2.

3.5 Issues relating to current clinical practice

As outlined in Section 3.2, there is a lack of treatment-specific recommendations for patients with R/M SCCHN who have progressed after platinum-based therapy, which is most likely reflective of the lack of head-to-head clinical trial data for currently-available therapies (see Section 4.10).[3, 15] Single-agent docetaxel is most routinely used in UK clinical practice, with methotrexate typically used for patients for whom docetaxel (or another taxane, such as paclitaxel) is not appropriate.[7] These treatments are considered to be palliative in nature, given the late stage of disease, and do not offer a convincing survival benefit to patients.[6, 7] The lack of alternative and effective therapies is indicative of the considerable unmet medical need for patients with R/M SCCHN who have progressed after platinum-based therapy.

3.6 Assessment of equality issues

No equality issues related to the use of nivolumab have been identified or are foreseen.

4 Clinical effectiveness

Summary of the clinical evidence

- Clinical evidence supporting the use of nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after receiving platinum-based therapy is presented from the pivotal phase III RCT CheckMate 141
- CheckMate 141 is an international, multicentre phase III RCT which provides direct head-to-head evidence across 361 patients randomised to either nivolumab 3 mg/kg Q2W (n=240) or IC of therapy (n=121; docetaxel n=54, methotrexate n=52, or cetuximab, n=15)
  - IC of therapy was used as comparator to reflect the lack of a single, universally-accepted therapy for the treatment of platinum-refractory R/M SCCHN when considering global treatment practices; investigators were to indicate their intended choice of therapy for their enrolled patients prior to randomisation
- Primary and secondary analyses were conducted for nivolumab versus the total IC arm

Summary of the clinical effectiveness results – CheckMate 141

- Nivolumab demonstrated significant improvements in OS relative to IC of therapy (HR 0.70 [97.73% CI, 0.51 to 0.96; p=0.0101]); corresponding to a 30% reduction in the risk of death with nivolumab versus IC of therapy
- Median OS was prolonged in the nivolumab arm (7.5 months; 95% CI, 5.5 to 9.1) compared to IC (5.1 months; 95% CI, 4.0 to 6.0)
  - 1-year survival was more than doubled in the nivolumab arm (36.0%) versus IC of therapy (16.6%)
- Median PFS was similar between treatment arms; however, a delayed separation of Kaplan-Meier curves in favour of nivolumab was observed (HR, 0.89; 95% CI, 0.70, 1.1; p=0.3236)
- ORR was more than doubled in the nivolumab arm (13.3%; 95% CI, 9.3, 18.3) compared to the IC arm (5.8%; 95% CI, 2.4, 11.6)
- Patient HRQoL in the nivolumab arm was stabilised, with no meaningful changes (≥10 points) across the majority of EORTC QLQ-C30 and QLQ-H&N35 scales in the first 21 weeks of follow-up; in contrast, meaningful declines in function and worsening of symptoms were reported for multiple domains in the IC arm
- Health problems, as measured by the EQ-5D-3L, were more prevalent in the IC arm than the nivolumab arm

Safety

- Nivolumab was generally well tolerated by patients in CheckMate 141 compared to IC of therapy
- The proportion of patients experiencing a drug-related, Grade 3-4 AE or SAE in the nivolumab arm was less than half that reported in the IC arm (drug-related, Grade 3-4 AEs: 13.1% nivolumab versus 35.1% IC of therapy; drug-related, Grade 3-4 SAEs: 4.7% nivolumab versus 10.8% IC of therapy); additionally, a lower proportion of patients discontinued treatment in the nivolumab arm versus the IC arm due to drug-related AEs of any grade (3.8% nivolumab versus 9.9% IC of therapy)
- 'Select' AEs did occur but were mostly Grade 1-2 and were generally manageable using the recommended treatment guidelines
- No new safety concerns with nivolumab were identified in CheckMate 141, with a similar safety/tolerability profile observed to that seen in trials of nivolumab monotherapy in other cancer types

4.1 Identification and selection of relevant studies

An SLR was conducted in November 2015 to identify relevant evidence on the efficacy and safety of nivolumab for the treatment of platinum-refractory R/M SCCHN. The SLR also included any approved and investigational interventions for the treatment of platinum-refractory R/M SCCHN, for the purposes of allowing a potential indirect treatment comparison with nivolumab. The original SLR was conducted in November 2015 and was subsequently updated in June and July 2016, in line with NICE guidance.

Search strategy

The SLR was performed using robust methodology in accordance with the methodological principles of conduct for systematic reviews as recommended by the Centre for Reviews and Dissemination (CRD)'s guidance for undertaking systematic reviews in health care, and the results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting checklist.[61, 62]

In the original SLR, the following online literature databases were searched from database inception to 20th November 2015:[i]

- MEDLINE® (including MEDLINE® In-Process)
- Embase®
- Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Methodology Register

The same online literature databases were searched for the SLR update and the same platforms were used to perform the searches with the exception of Embase®, MEDLINE®, MEDLINE® In-Process and MEDLINE® Epub ahead of print, which were searched via the Ovid SP platform. Search terms from the original SLR were translated and adapted as necessary for use in the Ovid SP platform (see Appendix 1 for full details of the search terms used for both the original SLR and the SLR update). For completeness, in the SLR update, a separate search was conducted in PubMed to identify any publications still listed as Epub ahead of print. Searches for the update were conducted on 7th June (PubMed), 8th June (Cochrane Library) and 18th July (Ovid SP). As the online literature databases in the original SLR were searched on 20th November 2015, date limits were used to restrict the online literature database searches for the SLR update to records published since 2015. The resulting records were then de-duplicated against the records from the original searches.

In addition to the online literature database searches, abstracts from the following conference proceedings were hand-searched for the preceding four years (2013 to 2015 in the original SLR, and 2016 in the SLR update):

- American Head and Neck Society (AHNS)
- American Society of Clinical Oncology (ASCO)
- European Society of Medical Oncology (ESMO)

[i] Embase® and MEDLINE® were searched via the Embase.com platform; MEDLINE® In-Process was searched via the PubMed.com interface; the Cochrane library was accessed using the Wiley Online Platform.

In the SLR update, abstracts from ASCO 2016 were also hand-searched; abstracts from AHNS 2016 and ESMO 2016 were not available at the time of updating the SLR.

Finally, in both the original SLR and the update SLR, the bibliographies of any SLRs or meta-analyses identified through the online literature database searches and the reference lists of any ultimately included studies were hand-searched for the identification of any further relevant trials.

Full details of the search strategies employed for both the original SLR and the SLR update are presented in Appendix 1.

Study selection

The titles and abstracts of all records identified in the original SLR were imported into a bespoke, structured query language-based internet database (and into EndNote for the SLR update) and duplicate records were excluded. The remaining titles and abstracts were then screened according to the inclusion/exclusion criteria presented in Table 6.

The same review process was followed for both the original SLR and the SLR update. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Full-texts were then obtained for any articles considered potentially relevant following the title and abstract screening, and these were reviewed according to the same inclusion/exclusion criteria presented in Table 6. In cases where the article did not provide enough information to be sure that it met the inclusion criteria, the article was excluded at the full-text screening stage to ensure that only relevant articles were ultimately included in the SLR. Both the title and abstract and the full-text screening were performed by two independent reviewers, with any disagreements resolved by a third independent reviewer, if necessary.

Table 6: Eligibility criteria used for both the original SLR and the SLR update

Domain	Inclusion Criteria	Exclusion Criteria
Population	• Adult patients (≥18 years) of any race and gender • At least 80% of patients were required to have been clinically diagnosed with advanced/metastatic (stage III/IV) SCCHN. • At least 80% of patients were required to be platinum-experienced • Studies which assessed a mixed population were included only if subgroup data for the relevant population were reported	• Studies focusing on children or adolescents were excluded. • Studies where patients were platinum-naïve, or platinum status was unclear were excluded
Intervention(s)	• Any approved or investigational intervention, including: • Nivolumab, docetaxel, methotrexate, fluorouracil, bleomycin, cisplatin, cetuximab, temoporfin, cabazitaxel, irinotecan, afatinib, zalutumumab, gefitinib, carboplatin, paclitaxel, lapatinib, bevacizumab, panitumumab, nimotuzumab, capecitabine, erlotinib, canertinib, MPDL3280A,	• Interventions not listed in the inclusion criteria, including radiotherapy, surgery and chemo-radiotherapy

Domain	Inclusion Criteria	Exclusion Criteria
	sorafenib, axitinib, buparlisib, MK-1775, pembrolizumab, MEDI4736, oxaliplatin, epirubicin, gemcitabine, vinorelbine, ifosfamide, pemetrexed, advexin, regorafenib • Combinations of any of the included interventions with a non-included intervention were also included.	
Comparator(s)	• Any active pharmacological agent • Therapy of investigator's choice • Placebo • Best supportive care	• Studies evaluating different doses of the same intervention (dose-ranging studies) will be excluded, if they do not include a placebo/best supportive care or active control comparison.
Outcomes	• Any efficacy outcomes • Any safety outcomes	• N/A
Study design	• Randomised controlled trials, including those with cross-over or parallel group designs • Non-randomised controlled trials • Single-arm, uncontrolled trials • Retrospective or prospective cohort studies • Case-control studies • Cross-sectional studies • Analyses of hospital records/databases • Systematic reviews or meta-analyses of relevant studies were included at the title and abstract screening stage for the purpose of identifying any additional studies not identified in the database searches, but were excluded at the full-text screening stage	• Case studies • Case series • Case reports
Publication type	• Journal articles, conference abstracts and presentations	• Comments, editorials, notes, letters and conference reviews
Other considerations	• Only full-text articles in the English language were included	

Abbreviations: N/A, not applicable; SCCHN, squamous cell carcinoma of the head and neck; SLR, systematic literature review.

Results

The PRISMA flow diagram of the evidence identified in the original and updated SLRs is presented in Figure 7.

- **Original SLR:** The original SLR yielded a total of 17,494 records, of which 1,402 records were excluded following the removal of duplicate records. A total of 14,559 records were then excluded following the title and abstract screening stage, and a total of 1,437 records were

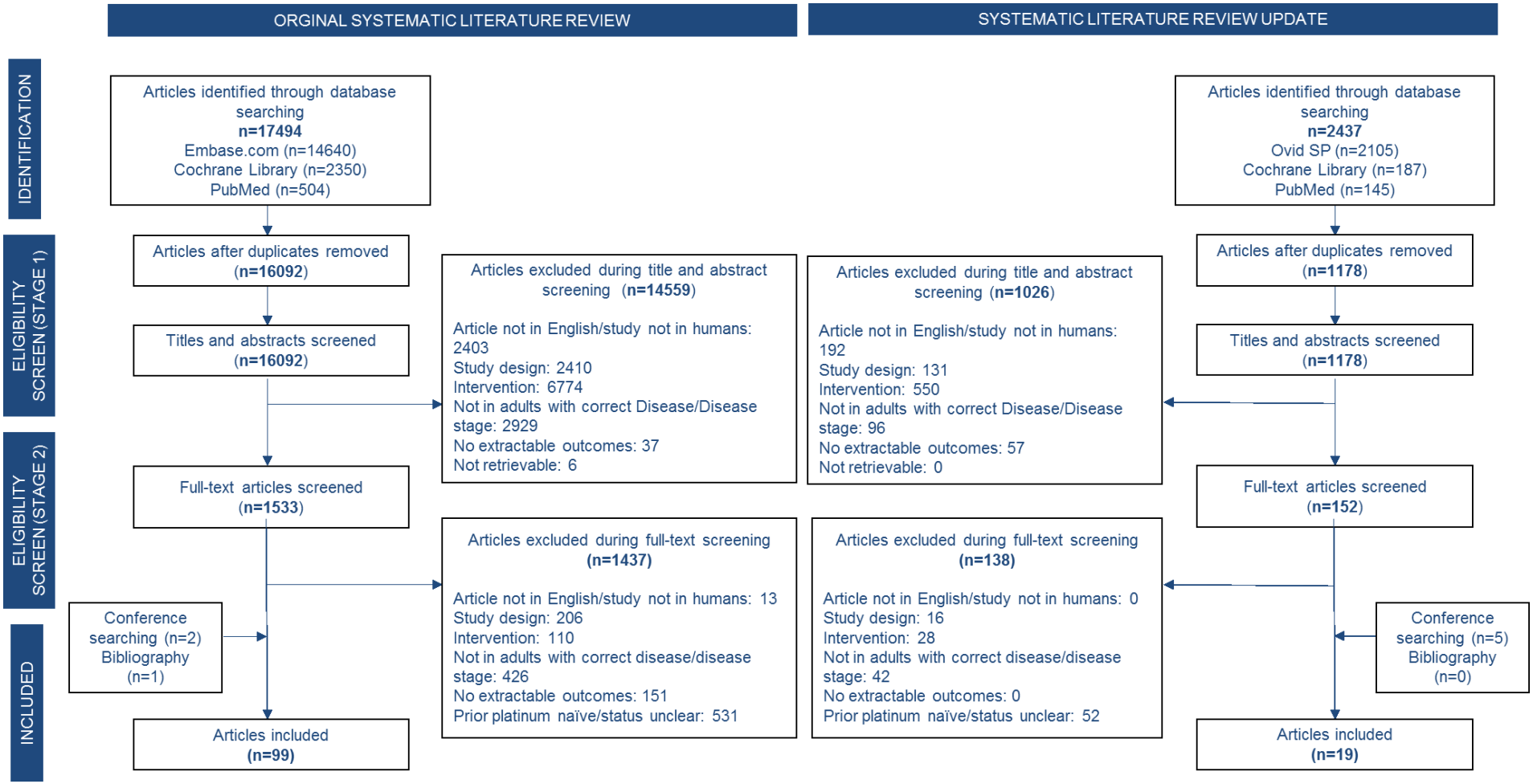
excluded following the full-text screening stage. An additional three relevant articles were identified from conference searching (n=2) and the bibliographies of included full-texts (n=1).

- **SLR update:** In the SLR update, a total of 2,437 records were identified in the searches, of which 1,259 records were excluded following the removal of duplicate records. A total of 1,026 records were then excluded following the title and abstract screening stage, and a total of 138 records were excluded following the full-text screening stage. An additional five relevant articles were identified from conference searching, whereas no additional relevant articles were identified from the bibliographies of included full texts.

As such, a total of 99 publications reporting on 66 unique studies were ultimately included in the original SLR, and in the SLR update, a total of 19 publications reporting on 13 unique studies were ultimately included. Overall, across both the original and the updated SLRs, a total of 118 publications on 77 unique studies were ultimately included, and a full list of these publications are presented in Appendix 2. In total, 1,575 records were excluded from the review at the full-text screening stage.

A review of the 118 ultimately included publications from both the original and the updated SLRs was then performed to identify any studies reporting data on the efficacy and safety of nivolumab for the treatment of adults with platinum-refractory R/M SCCHN, which would therefore be relevant to this submission. Only one study (CheckMate 141, NCT02105636) was identified following this review, which investigated the efficacy and safety of nivolumab versus IC of therapy, which consisted of monotherapy with either docetaxel, methotrexate or cetuximab. This study forms the principal evidence base for this submission and full details of this study are presented from Section 4.2 onwards.

Figure 7: PRISMA diagram for the clinical systematic literature review



Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

4.2 List of relevant randomised controlled trials

The clinical SLR identified one RCT (CheckMate 141, NCT02105636) that investigated the use of nivolumab as a treatment for adults with R/M SCCHN who have progressed after platinum-based therapy. CheckMate 141 was a phase III RCT, clinical evidence from which was presented as part of the regulatory submission to the EMA and from which a CHMP opinion is expected in ([redacted]) for the indication of R/M SCCHN after platinum-based therapy.

The SLR identified a single relevant article that reported evidence from the CheckMate 141 study (Ferris *et al.* [2016]).[9] A further article, Gillison *et al.* (2016),[8] presented at the 2016 American Association for Cancer Research annual meeting also reports evidence from the CheckMate 141 trial but was not captured in the clinical SLR. This specific conference was not hand-searched and articles from this conference are yet to be published online. Where possible, data are presented from these published sources – Ferris *et al.* (2016)[9] and Gillison *et al.* (2016)[8]; however, information presented in this submission has also been derived from the Clinical Study Reports (CSR) for CheckMate 141.[14]

An overview of CheckMate 141 is provided in Table 7, including details of the primary and secondary references used in this submission. In brief, adult patients with R/M SCCHN who had progressed on or within 6 months of the last dose of platinum-based therapy were randomised 2:1 to either nivolumab (3 mg/kg Q2W) or IC of therapy: docetaxel (30 mg/m^2 QW), methotrexate (40 mg/m^2 QW) or cetuximab (400 mg/m^2 once, then 250 mg/m^2 QW).[8, 14]

Table 7: List of relevant randomised controlled trials

Trial name	CheckMate 141 (NCT02105636)
Population	Adult patients with platinum-refractory R/M SCCHN
Intervention	Nivolumab (3 mg/kg, i.v. infusion, Q2W)
Comparator(s)	Investigator's choice: • Docetaxel (30 mg/m^2, i.v. infusion, QW) • Methotrexate (40 mg/m^2, i.v. infusion, QW) • Cetuximab (400 mg/m^2, i.v. infusion, once, then 250 mg/m^2, i.v. infusion, QW)
Primary study references	Gillison *et al.* (2016)[8] and Ferris *et al.* (2016)[9]
Secondary study reference(s)	CheckMate 141: CSR (7th June 2016)[14]

Only Ferris *et al.* (2016) was identified in the clinical SLR.

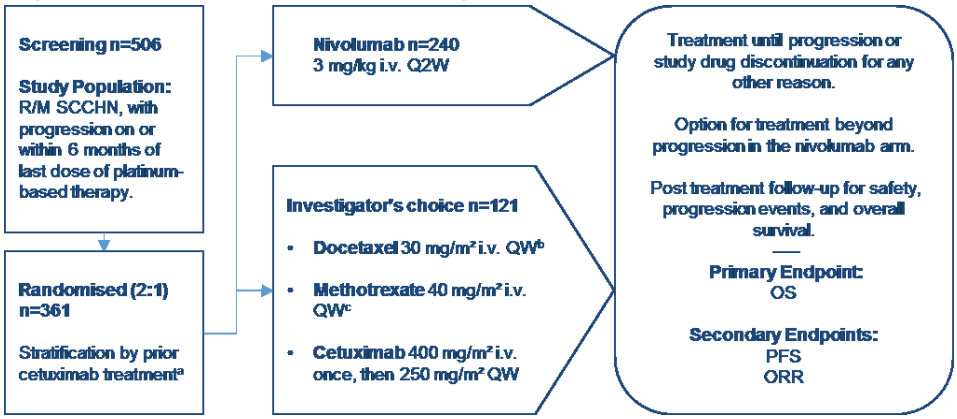
Abbreviations: CSR: Clinical Study Report; i.v., intravenous; Q2W: once every two weeks; QW: once weekly; R/M: recurrent or metastatic; SCCHN: squamous-cell carcinoma of the head and neck.

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 Trial design

CheckMate 141 is an international, multicentre, randomised, open-label, phase III trial that evaluated the efficacy and safety of nivolumab relative to IC of therapy (docetaxel, methotrexate or cetuximab) in adult patients with R/M SCCHN who had progressed after receiving platinum-based therapy. The CheckMate 141 trial design is illustrated in Figure 8.

Figure 8: CheckMate 141 trial design



[a] Prior cetuximab: Yes = 222 (61.5%), No = 139 (38.5%) (Case Report Form) [b] Docetaxel could be increased to 40 mg/m^2 if tolerated per local practices [c] Methotrexate could be increased to 60 mg/m^2 if tolerated per local practices
Dose reductions were not permitted for nivolumab, but were permitted for IC therapies
Exploratory endpoints investigated in CheckMate 141 included: DOR, TTR, HRQoL outcomes and safety

Abbreviations: DOR: duration of response; HRQoL: health-related quality of life; IC: investigator's choice; i.v.: intravenous; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; Q2W: once every two weeks; QW: once weekly; R/M: recurrent or metastatic; SCCHN: squamous-cell carcinoma of the head and neck; TTR: time to response.
Source: adapted from CheckMate 141 CSR (7th June 2016) – Figure 3.1-1[14]

The trial was initiated on the 29th May 2014 and in preparation for a protocol-specified, formal interim analysis of OS the clinical database was locked on the 18th December 2015.[14] Based on the results of this interim analysis, the independent DMC confirmed that the pre-specified statistical boundary for OS had been crossed (see Section 4.4), with no new safety concerns identified that would affect the continuation of the study; CheckMate 141 was therefore stopped early. Data presented in this submission are based on the latest available data cut-off points for each of the study outcomes: 18th December 2015 for patient disposition, OS, HRQoL and safety, 3rd February 2016 for PD-L1 analyses and 5th May 2016 for tumour assessments and subsequent therapies. Statistical considerations for the interim analysis of OS are provided in Section 4.4.

A full summary of the methodology of the CheckMate 141 trial is provided in Table 8.

Investigator's choice of therapy

Patients randomised to the IC arm received treatment with either docetaxel, methotrexate or cetuximab at the discretion of the investigator. In accordance with the trial protocol, investigators

were to indicate their intended choice of therapy for each patient (cetuximab, methotrexate or docetaxel) prior to randomisation.

IC of therapy was chosen as a comparator to reflect the lack of a single, universally-accepted therapy for the treatment of R/M SCCHN when considering global treatment practices (see Section 3.2). Docetaxel, methotrexate and cetuximab were selected in particular as these therapies appear to be the most active therapies for the treatment of platinum-refractory patients, have approved indications as single agents in the setting of R/M SCCHN, or represent a class of agents thought to be active in this setting (e.g. taxanes).[14] The majority of patients in the IC arm who received at least one dose of study treatment were treated with either docetaxel (47%) or methotrexate (41%), with the remaining 12% of patients receiving cetuximab.[8] Expert clinical opinion is that the three therapies used in the IC arm can be considered equivalent in terms of survival outcomes (see Section 3.2).[6]

Treatment beyond progression

In Checkmate-141, patients were treated with study drug until disease progression, unacceptable toxicity, or other protocol-defined reasons (e.g. withdrawal of consent).

Patients in the nivolumab arm were permitted to continue treatment beyond initial Response Evaluation Criteria In Solid Tumours (RECIST)-defined progression if the investigator deemed that they were experiencing clinical benefit and were tolerating the study drug. This is consistent with the licensed posology for nivolumab which states that "*treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient*."[13] The rationale for permitting treatment beyond initial RECIST-defined progression was based on accumulating evidence indicating that a minority of subjects treated with immune-checkpoint inhibitors may derive clinical benefit despite initial evidence of disease progression (see Section 2.1).[14, 63]

The duration of study drug treatment in each treatment group is detailed in Section 4.12.

Table 8. Summary of CheckMate 141 trial methodology

Trial name	CheckMate 141
Location	International: 55 study sites across 15 countries in North America (USA and Canada), South America, Europe and Asia[14] Five study sites were included in the UK, with a total of 34 patients randomised to study treatment at UK sites[14]
Trial design	Multicentre, open-label, phase III randomised controlled trial
Method of randomisation	Patients were randomised (2:1) to receive either nivolumab or IC of therapy, with stratification by prior cetuximab treatment (yes or no). Randomisation was conducted using a centralised interactive voice response system (IVRS). The investigator's intended choice of therapy (docetaxel, methotrexate or cetuximab) was entered in the IVRS for every patient prior to randomisation.
Eligibility criteria for participants	**Key inclusion criteria**: • Males and females ≥18 years of age with an ECOG performance status of 0 or 1 • Histologically confirmed R/M SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) • Tumour progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant, primary, recurrent, or metastatic setting

Trial name	CheckMate 141
	• Measurable disease by CT or MRI per RECIST 1.1 criteria[64] • Documentation of p-16 positive or p-16 negative disease to determine HPV-p16 status of tumour for SCCHN of the oropharynx • Availability of tumour samples for PD-L1 expression analysis **Key exclusion criteria**: • Active, known or suspected autoimmune disease • Systemic treatment with either corticosteroids or other immunosuppressive medications (within 14 days of study drug administration) • Active brain metastases or leptomeningeal metastases • Histologically confirmed R/M carcinoma of the nasopharynx, SCC of unknown primary, and salivary gland or non-squamous histologies (e.g. mucosal melanoma) • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways A full list of inclusion and exclusion criteria is presented in Table 9.
Settings and locations where the data were collected	Data were collected in accordance with Good Clinical Practice by trained and qualified investigators using a single protocol to promote consistency across the multiple study sites. An independent DMC was established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio. The DMC acted in an advisory capacity to the study sponsor, monitoring patient safety and evaluating the available efficacy data for the study.
Trial drugs and method of administration	**Nivolumab group (n=240)** • Nivolumab, i.v. infusion, 3 mg/kg, Q2W Four patients randomised to the nivolumab arm did not receive ≥1 dose of study treatment. **Investigator's choice (n=121)** Patients were randomised to the IC arm and received one of the three possible therapies at the discretion of the investigator (see list below). Investigators were to indicate their intended choice of therapy for each patient prior to randomisation. • Docetaxel (30 mg/m^2, i.v. infusion, QW) (n=54)[a] • Methotrexate (40 mg/m^2, i.v. infusion, QW) (n=52)[b] • Cetuximab (400 mg/m^2, i.v. infusion, once, then 250 mg/m^2, i.v., QW) (n=15)[c] Ten patients randomised to the IC arm did not receive ≥1 dose of study treatment. Treatment in both arms was continued until progression, unacceptable toxicity, or withdrawal of consent. Patients in the nivolumab arm were permitted to continue treatment beyond investigator-assessed RECIST 1.1-defined progression if they were experiencing a clinical benefit, as determined by the investigator, and were tolerating the study drug. Dose reductions were not permitted for nivolumab but were allowed for therapies in the IC arm. Dose delays were permitted in both trial arms.

Trial name	CheckMate 141
Permitted and disallowed concomitant medication	The following medications were prohibited during the study: • Immunosuppressive agents (except to treat a drug-related adverse event) • Systemic corticosteroids >10 mg daily prednisone equivalent[d] • Any concurrent anti-neoplastic therapy Supportive care for disease-related symptoms was permitted for all patients in the trial. Surgical resection of solitary lesions and palliative radiotherapy were permitted during the trial if certain protocol-defined criteria were met.[14] Prior palliative radiotherapy must have been completed at least 2 weeks before study drug administration.
Primary outcomes	**Overall survival (OS)** Patients were followed up continuously whilst on study treatment and then every 3 months until death, loss to follow-up, or withdrawal of study consent after patients discontinued study treatment.
Secondary and other outcomes	**Secondary endpoints:** • Progression-free survival (PFS) • Objective response rate (ORR) **Exploratory endpoints:** • Duration of response (DOR) • Time to response (TTR) • Safety • Patient-reported outcomes (PROs) assessed using EORTC QLQ-C30 and QLQ-H&N35 questionnaires, as well as the EQ-5D-3L questionnaire A full description of outcomes is presented in Table 10. **Timing of assessments:** • Tumour assessments were scheduled every 6 weeks as of Week 9 until disease progression or treatment discontinuation (whichever occurred last). Assessments were performed using CT or MRI and included the head and neck, chest, abdomen and all known sites of disease. Changes in tumour responses were determined by the investigator and assessed according to RECIST 1.1.[64] • AEs were assessed during treatment visits and were included in safety analyses if they occurred within 30 days from the day of the last dose received. • HRQoL was assessed before each dose at Week 1, then every 6 weeks as of Week 9. Two follow-up visits and subsequent survival follow-up visits were also scheduled (AEs and PROs)[e]
Subgroups	A pre-planned exploratory subgroup analysis of OS by treatment group and PD-L1 expression (≥1% or <1%) was conducted. In addition, the following exploratory analyses were added after database lock to help further characterise the study results: • OS of nivolumab versus IC by HPV-p16 status (positive or negative) • OS of nivolumab versus IC by selected demographic and baseline characteristics, including intended therapy for the IC arm Full details of subgroup analyses are presented in Section 4.8.
Duration of study and follow-up	The study was initiated on the 29th May 2014 with the last patient last visit on 6th November 2015 and the clinical database locked on the 18th December 2015.

Trial name	CheckMate 141
	At this data cut-off point, the median duration of follow-up was 5.3 months (range, 0.0–16.8) and 4.6 months (range, 0.0–15.2) in the nivolumab and IC arms, respectively.

[a] Dose of docetaxel could be increased to 40 mg/m^2 if tolerated, as per local practices
[b] Dose of methotrexate could be increased to 60 mg/m^2 if tolerated, as per local practices
[c] Cetuximab was only administered where approved for use as a monotherapy for recurrent SCCHN
[d] Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents were permitted in the absence of active autoimmune disease
[e] Follow-Up Visit 1 was scheduled for 35 days from the last dose ±7 days or coincided with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose. Follow-Up Visit 2 was scheduled for 80 days (±7 days) from Follow-Up Visit 1. Survival follow-up visits were scheduled for every 3 months (± 7 days) from Follow-Up Visit 2.

Abbreviations: AEs: adverse events; CT: computerised tomography; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; DMC: Data Monitoring Committee; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30 and H&N35: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and Head and Neck 35; EQ-5D-3L: 3-level EuroQoL 5-Dimensions; HPV: human papillomavirus; i.v., intravenous; IC: investigator's choice; IVRS: interactive voice response system; ORR: objective response rate; OS: overall survival; PD-L1: programmed death ligand 1; PFS: progression-free survival; PROs: patient-reported outcomes; Q2W: once every two weeks; QW: once weekly; RECIST: Response Evaluation Criteria In Solid Tumours; R/M: recurrent or metastatic; SCCHN: squamous-cell carcinoma of the head and neck; TTR: time to response.
Source: Gillison *et al.* (2016)[8] and CheckMate 141 CSR (7th June 2016)[14]

4.3.2 Eligibility criteria

The full eligibility criteria for enrolment in CheckMate 141 are provided in Table 9.

Adult patients were considered for enrolment if they had histologically confirmed R/M SCCHN (oral cavity, pharynx [except nasopharynx], larynx), that was not amenable to local therapy with curative intent, and had experienced tumour progression or recurrence within six months of the last dose of platinum-based therapy.

Table 9: Eligibility criteria for CheckMate 141

Inclusion criteria	Exclusion criteria
Signed Written Informed Consent • Patients must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines • Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study **Target Population** • Histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) • ECOG performance status of 0 or 1 • Documentation of p16-positive or p16-negative disease to determine HPV-p16 status of tumour for SCCHN of the oropharynx • Tumour progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (i.e. with radiation after surgery), primary (i.e. with radiation), recurrent, or metastatic setting. Clinical progression after platinum therapy is an allowable event for entry and is defined as progression of a lesion at least 10 mm in size that is amenable to caliper measurement (e.g. superficial skin lesion as per RECIST 1.1) or a lesion that has been visualized and photographically recorded with measurements and shown to have progressed. • Measurable disease by CT or MRI per RECIST 1.1 criteria • Tumour tissue (archival or fresh biopsy specimen) must be available for PD-L1 expression analysis and other biomarker correlative studies • Prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration. • Immunosuppressive doses of systemic medication, such as steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration	**Target Disease Exceptions** • Active brain metastases or leptomeningeal metastases are not allowed. Patients with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (except where contraindicated in which CT scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. Cases, including base of skull lesions without definitive evidence of dural or brain parenchymal involvement, should be discussed with the medical monitor. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. • Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx, squamous-cell carcinoma of unknown primary, and salivary gland or non-squamous histologies (e.g. mucosal melanoma) are not allowed. **Medical History and Concurrent Diseases** • Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the patient to receive protocol therapy, or interfere with the interpretation of study results. • Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous-cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast. • Patients with active, known or suspected autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol. • Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement

Inclusion criteria	Exclusion criteria
except as noted in the exclusion criteria. • Screening laboratory values must meet the following criteria (using CTCAE v4) and should be obtained within 14 days prior to randomization: ○ WBC ≥2000/μL ○ Neutrophils ≥1500/μL ○ Platelets ≥100 x103/μL ○ Haemoglobin ≥9.0 g/dL ○ Serum creatinine ≤1.5 x ULN or creatinine clearance (CrCl) >40 mL/min (using the Cockcroft-Gault formula): ○ AST/ALT ≤3 x ULN ○ Total bilirubin ≤1.5 x ULN (except patients with Gilbert Syndrome, who can have total bilirubin <3.0 mg/dL) ○ Calcium levels must be normalized and maintained within normal limits for study entry and on treatment. Medical management of calcium levels is permitted ○ Patients with an initial magnesium <0.5 mmol/L (1.2 mg/dL) may receive corrective magnesium supplementation but should continue to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) at the investigator's discretion • Patients must have resting baseline O_2 saturation by pulse oximetry of ≥92% at rest **Patient Re-enrolment** • This study permits the re-enrolment of a patient that has discontinued the study as a pre-treatment failure (i.e. patient has not been randomised / has not been treated). If re-enrolled, the patient must be re-consented. **Age and Reproductive Status** • Males and Females, ≥18 years of age. • Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug	doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways • All toxicities attributed to systemic prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Patients with toxicities attributed to systemic prior anti- cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enrol. • Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (patients with prior radiation, cytotoxic or investigational products <4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 4). **Physical and Laboratory Test Findings** • Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. Patients who test positive for HCV antibody but negative for HCV ribonucleic acid are permitted to enrol. • Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) • Any Grade 4 laboratory abnormalities **Allergies and Adverse Drug Reaction** • History of allergy to study drug components • History of severe hypersensitivity reaction to any human monoclonal antibody **Other Exclusion Criteria** • Prisoners or patients who are involuntarily incarcerated • Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness

Inclusion criteria	Exclusion criteria
• Women must not be breastfeeding • WOCBP must agree to follow instructions for method(s) of contraception from the time of enrolment for the duration of treatment with study drug(s) plus 5 half-lives of study drug(s) plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post treatment completion. • Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half- lives of study drug(s) plus 90 days (duration of sperm turnover) for a total of 31 weeks post treatment completion. • Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they still must undergo pregnancy testing as described in these sections.	

Abbreviations: AIDS: acquired immunodeficiency syndrome; AST/ALT: aspartate aminotransferase/ alanine aminotransferase; CrCl: creatinine clearance; CT: computerised tomography; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; ECOG: Eastern Cooperative Oncology Group; HBV sAg: hepatitis B virus surface antigen; HCG: human chorionic gonadotropin; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HPV: human papillomavirus; IRB/IEC: Institutional Review Board/Institutional Ethics Committee; MRI: magnetic resonance imaging; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PD-1: programmed death 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2; RECIST: Response Evaluation Criteria In Solid Tumours; SCCHN: squamous-cell carcinoma of the head and neck; ULN: upper limit of normal; WBC: white blood cell; WOCBP: women of childbearing potential.
Source: CheckMate 141 CSR (7th June 2016)[14]

4.3.3 CheckMate 141 study endpoints

Detailed descriptions of the study outcomes assessed in CheckMate 141 are provided in Table 10 alongside the methods of assessments.

Primary and secondary endpoints

The primary endpoint of CheckMate 141 was OS, defined as the time from randomisation to the date of death from any cause. OS is the most relevant and meaningful clinical outcome for patients with R/M SCCHN and their families, as these patients are often considered as being at an end-of-life stage with currently available therapies (see Section 3.3). Furthermore, OS represents the gold standard for demonstrating the clinical benefit of anti-cancer therapies, as recognised by guidelines from the EMA.[65] Secondary outcomes assessed in CheckMate 141 included PFS and ORR. Tumour responses and disease progression were determined by the investigator and assessed using RECIST version 1.1, as is recommended for clinical trials of anti-cancer therapies.[64, 65]

It should be noted that although the RECIST criteria are well-established for use in clinical trials of anti-cancer therapies, RECIST may have limitations as a method of evaluating clinical benefit in terms of response or progression with immune-checkpoint inhibitors. This is because patients who ultimately derive clinical benefit from immunotherapy may progress by RECIST criteria before exhibiting a response (see Section 2.1, Figure 4). The relationship between RECIST response and clinical benefit remains poorly understood. Nevertheless, RECIST remains the imaging criteria accepted by regulatory agencies, and a more appropriate immunotherapy-specific evaluation technique has not yet been developed.

Exploratory endpoints

The time to either a complete or partial tumour response (TTR) and the duration of response (DOR) were assessed as exploratory outcomes in CheckMate 141. In addition, patient-reported outcomes (PROs) and safety were included as exploratory outcomes.

As part of the safety review, particular attention was paid to the identification and assessment of 'Select' AEs which were immune-related and potentially associated with the use of nivolumab. PROs were assessed using validated HRQoL instruments, including the EORTC QLQ-C30 questionnaire that is commonly used in cancer trials and the disease-specific EORTC QLQ-H&N35 questionnaire.[49, 66] General health status was also assessed using the EQ-5D-3L questionnaire that is favoured by NICE as a source of utility data.[25, 67] Given that the palliation of symptoms, control of disease and treatment tolerability are key aims and considerations for treatment at the R/M disease stage (see Section 3.1), these exploratory outcomes are also relevant for the patient population considered as part of this appraisal.

Table 10: Description of outcomes reported in CheckMate 141

Outcome	Description and method of assessment
Primary:	
Overall survival (OS)	OS was defined as the time from randomisation to the date of death from any cause. The survival time for patients who had not died was censored at the last known alive date. OS was censored at the date of randomisation for patients who were randomised but had no follow-up.

Outcome	Description and method of assessment
	Patients were followed up continuously whilst on study treatment and then every 3 months until death, loss to follow-up, or withdrawal of study consent after patients discontinued study treatment.
Secondary:	
Progression-free survival (PFS)[a]	PFS was defined as the time from randomisation to first date of documented progression, as determined by the investigator (as per RECIST 1.1 criteria), or to death due to any cause, whichever occurred first. • Patients who neither progressed nor died were censored on the date of their last tumour assessment on study • Patients who did not have any on-study tumour assessments and did not die were censored on their date of randomisation • Patients who received subsequent systemic anti-cancer therapy prior to progression were censored at the date of their last tumour assessment on or prior to secondary therapy
Objective response rate (ORR)[a]	ORR was defined as the proportion of randomised patients who achieved a best overall response (BOR) of complete response (CR) or partial response (PR), based on RECIST 1.1 criteria, as per investigator assessment. BOR was defined as the best response designation, recorded between the date of randomisation and the date of progression, as assessed by the investigator per RECIST 1.1, or the date of subsequent anti-cancer therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurred first. For patients who continued treatment beyond progression, the BOR was determined based on response assessments up to the time of initial RECIST 1.1 progression.
Exploratory:	
Duration of response (DOR)[a,b]	DOR was defined as the time between the date of first confirmed response (CR or PR) to the date of the first documented progression as determined by the investigator (per RECIST 1.1), or death due to any cause, whichever occurred first. For patients who neither progressed nor died, the duration of response was censored at the same time they were censored for PFS. DOR was evaluated for responders (i.e. patients with confirmed CR or PR) only.
Time to response (TTR)[a]	TTR was defined as the time from randomisation to the date of the first response (CR or PR), as assessed by the investigator. TTR was evaluated for responders (i.e. patients with a BOR of confirmed CR or PR) only.
Safety	The assessment of safety was based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, and abnormalities in specific clinical laboratory assessments. 'Select' AE analyses included incidence, time-to-onset, and time-to-resolution. Analyses were conducted using the 30-day and 100-day safety window from day of last dose received. AEs were coded using the MedDRA Version 18.1. AEs and laboratory values were graded for severity according to the NCI CTCAE version 4.0.
EORTC QLQ-C30 and QLQ-H&N35	The **EORTC QLQ-C30** has 30 items divided among 5 functional scales (physical, role, emotional, social, and cognitive), 3 multi-item symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and 6 single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The two items measuring overall health status and quality of life are graded on a 7-

Outcome	Description and method of assessment
	point Likert scale, while all remaining items are graded on a 4-point scale: 1 (not at all) to 4 (very much). The **EORTC QLQ-H&N35** is a 35-item instrument grouped into 7 multi-item scales (pain, swallowing, sensory problems, speech problems, trouble with social eating, trouble with social contact, and reduced sexuality) and 11 single-item scales (teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, and weight gain). 30 items are graded on a 4-point scale and 5 items utilise a binary response set (yes/no). For each item, raw scores were transformed to a 0–100 scale with higher scale scores representing better functioning or HRQoL (functional and global health status/HRQoL scales) or worsening of symptoms (symptom scales). A clinically meaningful change in score was regarded as a change in ≥10 points.[21, 68]
EQ-5D	The EQ-5D is a standardised instrument used to measure self-reports of general health status. The **EQ-5D-3L** descriptive system is comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, moderate problems, and extreme health problems. The **EQ- 5D VAS** recorded the patient's self-rated health state on a 100-point vertical VAS (0 = worst imaginable health state; 100 = best imaginable health state). For the EQ-5D VAS, a change in seven points was regarded as clinically meaningful.[69]

[a] The first on-study tumour assessment was scheduled at Week 9 (±1 week) following randomisation. Subsequent tumour assessments were scheduled every 6 weeks (±1 week) until disease progression.
[b] DOR data were not available at the time of submission (see Section 4.14)

Abbreviations: AEs: adverse events; BOR: best overall response; CR: complete response; DOR: duration of response; EORTC QLQ-C30 and H&N35: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and Head and Neck 35; EQ-5D-3L: 3-level EuroQol 5-Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria In Solid Tumours; SAEs: serious adverse events; TTR: time to response; VAS: Visual Analogue Scale.
Source: CheckMate 141 CSR (7th June 2016)[14]

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

A total of 361 patients were enrolled in CheckMate 141 and randomised to receive either nivolumab or IC of therapy.[8] The study populations used in the analysis of primary and secondary outcomes are presented in Table 11.

Table 11: Study populations used for the analysis of outcomes in CheckMate 141

Analysis	Study population
All-randomised population	All enrolled patients who were randomised to study arms (intention-to-treat). The all-randomised population was used for the analysis of efficacy outcomes, including OS. • Nivolumab arm (n=240) • IC of therapy arm (n=121)
All-treated population	All randomised patients who received at least one dose of study drug. The all-treated population was used for safety analyses and dosing evaluation. • Nivolumab arm (n=236) • IC of therapy arm (n=111)

Abbreviations: IC: investigator's choice
Source: Gillison *et al.* (2016)[8] and CheckMate 141 CSR (7th June 2016)[14]

Primary analysis

The primary objective of CheckMate 141 was to compare OS between treatment arms in all randomised patients. A summary of the statistical tests used in the primary analysis of OS is presented in Table 12 alongside sample size calculations and methods for handling missing data.

An interim analysis for OS was planned for when at least 195 deaths (70% of deaths required to have 90% power to detect a HR of 0.6667; see Table 12) had occurred, with the nominal stopping boundary for OS based on the actual number of events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. At the clinical database lock on 18th December 2015, the pre-specified number of events observed had been reached, with a total of 218 patients randomised to study treatment having died (78% of deaths required).[8] On review of the interim data, the DMC confirmed that the pre-specified boundary for OS (nominal significance level p≤0.0227) had been crossed, with no new safety concerns identified that would affect the continuation of the study. Based on the results of this review, the DMC decided that the study could be stopped early with nivolumab having met the primary endpoint.

The sample size calculations that informed the CheckMate 141 trial design were conducted to ensure that the trial was sufficiently powered to detect differences in OS between treatment arms (nivolumab versus IC of therapy). The trial was therefore not designed to detect differences between nivolumab and the individual therapies that comprise the IC arm. The sample size for each individual therapy was relatively small in the IC arm, with 52, 46 and 13 patients, respectively, receiving at least one dose of docetaxel, methotrexate or cetuximab. Moreover, randomisation procedures did not hold in the assignment of patients to each of the three individual therapies comprising the IC arm, with the choice of intended IC therapy made at the investigator's discretion prior to randomisation. Thus, analysis of outcomes by therapies in the IC arm may be at risk for selection bias for observable and unobservable patient characteristics. Consequently, the main clinical effectiveness results presented in this submission are for comparisons between nivolumab and the IC arm as a whole.

Subgroup analyses of OS by intended therapy for the IC arm are presented in Section 4.8. However, the small sample sizes, lack of statistical power and the breaking of randomisation should be taken into account when considering these subgroup analyses by intended therapy for the IC arm.

Table 12: Statistical methods for the primary analysis of CheckMate 141

Trial name	CheckMate 141
Hypothesis objective	Nivolumab will improve OS as compared to IC for patients with platinum-refractory R/M SCCHN
Statistical analysis	OS was analysed in the all-randomised population. Median OS was estimated using the Kaplan-Meier method with 95% CI computed for each treatment arm based on the log-log transformation (Brookmeyer-Crowley method). A log-rank test stratified by prior cetuximab therapy (yes or no), as reported in the IVRS, was used to compare OS between patients in the nivolumab and IC arms. Hazard ratios and corresponding CIs were estimated using a stratified Cox proportional hazards model, with treatment arm as a single covariate.
Sample size, power calculation	The number of events and power of this study was calculated assuming an exponential distribution for OS in each arm. The alpha level for OS was adjusted for one planned interim analysis. The study required at least 278 deaths to ensure that a 2-sided, α=0.05 level, sequential log-rank test procedure with one interim look after 70% of deaths (195 deaths) had 90% power when the true OS hazard ratio of the experimental to the control arm was 0.6667. This is equivalent to demonstrating a 50% improvement in median OS in the nivolumab group (9 months) relative to the IC group (6 months). Based on the required number of events, approximately 360 patients were to be randomised.
Data management, patient withdrawals	For patients who were alive, OS was censored at the last date of contact. For patients who were randomised but had no follow-up, OS was censored at the date of randomisation.

Abbreviations: CI: confidence intervals; IC: investigator's choice; IVRS: interactive voice response system; OS: overall survival; R/M: recurrent or metastatic; SCCHN: squamous-cell carcinoma of the head and neck.
Source: CheckMate 141 CSR (7th June 2016)[14]

Statistical methods for additional analyses

A hierarchical testing procedure was used for the comparisons of secondary endpoints to preserve the study-wise type I error rate at 0.005. If a statistically significant improvement in OS was demonstrated for nivolumab compared with IC, then PFS would be compared between treatment arms at the 5% level. Similarly, ORR would only be compared between-arms at the 5% significance level if significant improvements in PFS were observed.

As with OS, median PFS was estimated using the Kaplan-Meier method, with a log-rank test stratified by prior cetuximab therapy (yes or no), as reported in the interactive voice response system (IVRS), used for between-arm comparisons. Patients were censored a) at the date of their last evaluable tumour assessment if they did not progress or die, b) at the date of randomisation if they did not have any on-study tumour assessments, or c) at the date of the last tumour assessment prior to the initiation of subsequent systemic anti-cancer therapy if they received this new therapy prior to documented progression. Patients who died without a reported progression were considered to have progressed on the date of their death.

The comparison of response rate between treatment arms was conducted using a two-sided Cochran-Mantel-Haenszel test, again stratified by prior cetuximab therapy (yes or no), as reported in the IVRS. Estimates of response rate, along with exact two-sided 95% CI were computed within each treatment arm. For PROs, data were analysed as mean changes from baseline scores. Minimal important differences were used to calculate the proportion of patients

that experienced clinically meaningful deterioration over time, defined as a 10-point change in scores from baseline.[21, 68]

4.5 Participant flow in the relevant randomised controlled trials

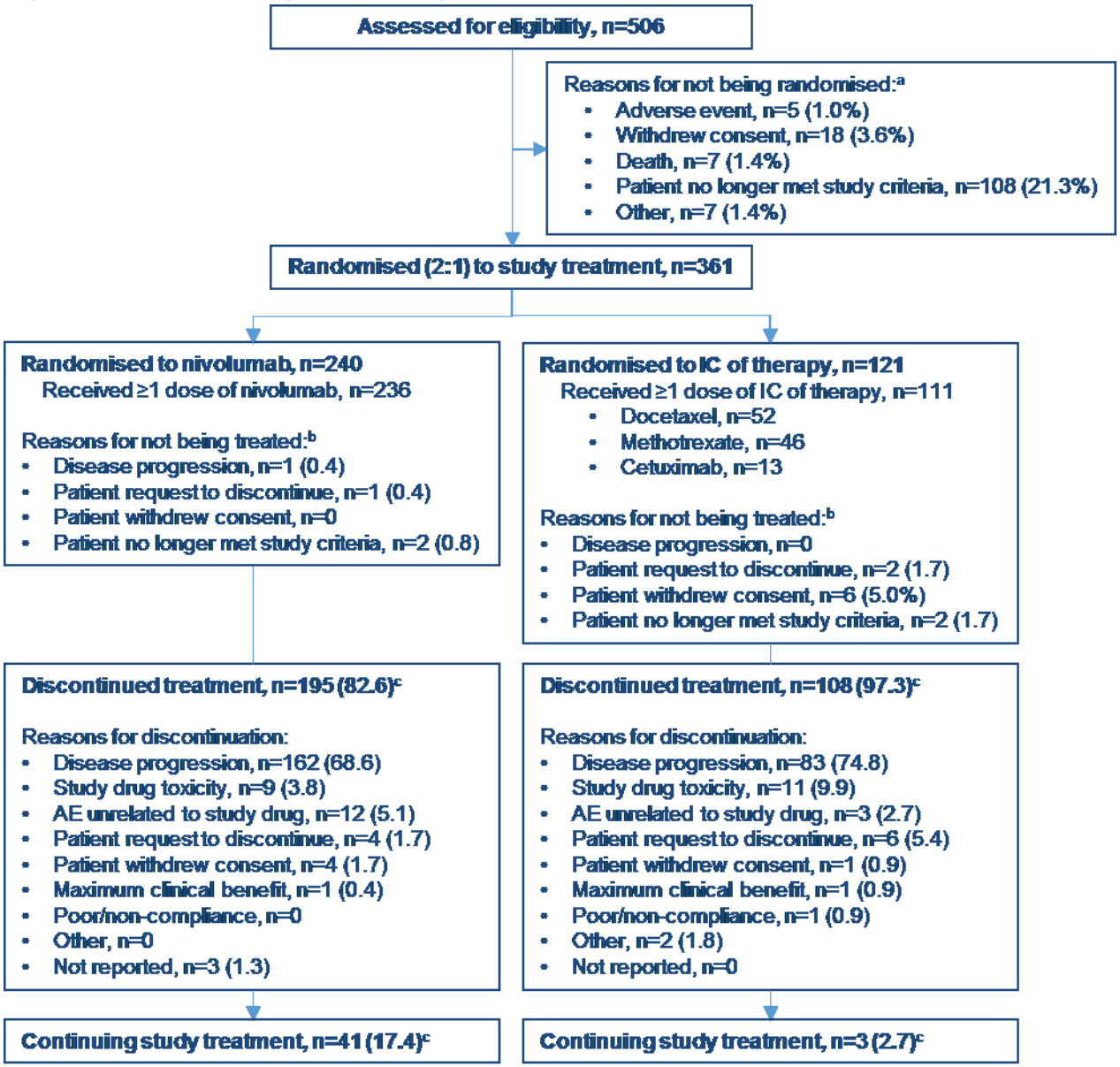
4.5.1 Participant flow in CheckMate 141

A total of 361 patients were randomised in CheckMate 141, thus comprising the all-randomised population. Fourteen patients (four in the nivolumab arm and ten in the IC arm) were randomised but did not receive at least one dose of study drug, and were thus excluded from the all-treated population.[8] The all-treated population consequently comprised 96.1% of the all-randomised population.

All patients randomised to the IC arm who received study treatment (111/121 patients) received the intended regimen as indicated by the investigator prior to randomisation; no patient received a different IC therapy at study entry to that which was intended for them prior to randomisation. In total, 54, 52 and 15 patients were randomised to docetaxel, methotrexate and cetuximab, respectively, with 52, 46 and 13 patients receiving at least one dose of respective study treatment.[8, 14] Therefore, of the 10 patients randomised to IC who did not receive treatment, 2 were intended to receive docetaxel, 6 were intended to receive methotrexate and 2 were intended to receive cetuximab.

At the data cut-off point, a total of 41 (17.4%) and 3 (2.7%) patients in the all-treated population were continuing study treatment in the nivolumab and IC arms, respectively.[8] At this point, a total of 218 deaths had occurred – 133 in the nivolumab arm (55.4% of patients) and 85 in IC arm (70.2% of patients).[8] Full details of participant flow, including the reasons for treatment discontinuation, are presented in the CONSORT diagram in Figure 9.

Figure 9: CONSORT diagram showing patient flow in CheckMate 141



Percentages given in brackets: [a] percentage of all-enrolled patients; [b] percentage of all-randomised patients; [c] percentage of all-treated patients. Database lock of 18th December 2015.

Abbreviations: AE: adverse event; CONSORT: Consolidated Standards of Reporting Trials; IC: investigator's choice.
Source: CheckMate 141 CSR (7th June 2016) – Table 5.1-1 and Table S.2.5[14]

4.5.2 Subsequent therapies received in CheckMate 141

As of the latest database lock on the 5th May 2016, subsequent anti-cancer therapy was received by 35.0% and 38.0% of patients in the nivolumab and IC arms, respectively, with 29.6% and 32.2% of patients in each arm receiving subsequent systemic therapy.[14] In the nivolumab arm, 9.6%, 7.1% and 4.2% of patients received subsequent systemic therapy with cetuximab, methotrexate and docetaxel, respectively.[14] In the IC arm, 7.4% of patients received subsequent systemic therapy with an anti-PD-1 pathway agent (0.8% received nivolumab and 6.6% received pembrolizumab).[14]

A complete list of subsequent therapies received by treatment group is presented in Appendix 3.

4.5.3 Baseline characteristics

Baseline demographics, disease characteristics and a summary of prior therapies for each treatment arm (nivolumab and IC) are presented in Table 13. Patient characteristics were generally well-balanced, although there was a higher proportion of former/current smokers in the nivolumab arm (79.6%) compared to the IC arm (70.2%).[8] Prior cetuximab treatment (yes or no), which was the only stratification factor at randomisation, was balanced between treatment arms, with the majority of patients in the nivolumab (62.5%) and IC arms (59.5%) having received prior cetuximab (Case Report Form).[14] All randomised patients had received prior systemic treatment with platinum-based therapy as per the anticipated indication for nivolumab as a treatment for R/M SCCHN. Of those patients randomised to study treatment, 190 patients (52.6%) had not received prior systemic therapy for metastatic disease (the remainder having received prior systemic therapy in the adjuvant, neo-adjuvant or primary setting), raising the possibility that patients may receive platinum-based therapy at an earlier stage of disease in clinical practice (see Section 3.2).

Patients randomised to receive study treatment in CheckMate 141 were typically male (83.1%), white (83.1%) and former/current smokers (76.5%); the median age of patients was 60 years. This patient population is generally consistent with that of patients expected to present with SCCHN in UK clinical practice, as described in Section 3.1.

HPV-p16 status at randomisation was recorded for a total of 178 patients (49.3%), with 92 (25.5%) and 86 (23.8%) of all randomised patients having p16-positive and p16-negative disease, respectively.[14] As stipulated by the study protocol, investigators were instructed to test the HPV-p16 status of patients with oropharyngeal disease. The collection of tumour tissue specimens prior to study entry was also stipulated in the study protocol in order to enable the analysis of efficacy according to PD-L1 expression to be conducted. At the PD-L1 database lock of 3rd February 2016, the majority of randomised patients (90.6%) had a tumour biopsy collected, with 260 (72.0%) of all randomised patients having quantifiable PD-L1 expression at baseline.[8] Of these 260 patients, 149 patients (57.3%) had PD-L1 expression ≥1% and 111 patients (42.7%) had PD-L1 expression <1%.[8]

Baseline demographics, disease characteristics and a summary of prior therapies for the nivolumab arm and each individual therapy in the IC arm are presented in Appendix 4. No patients enrolled at a European study site who were randomised to the IC arm received cetuximab, reflecting the fact that single-agent cetuximab is not licensed for use in R/M SCCHN.[70]

Table 13: Baseline characteristics of patients in the all-randomised population in CheckMate 141

Characteristic	Nivolumab (n=240)	IC (n=121)	Total (N=361)
Demographics			
Age, median years (range)	59.0 (29–83)	61.0 (28–78)	60.0 (28–83)
Age categorisation, n (%)			
<65	172 (71.7)	76 (62.8)	248 (68.7)
≤65 and <75	56 (23.3)	39 (32.2)	95 (26.3)
≥75	12 (5.0)	6 (5.0)	18 (5.0)
Male, n (%)	197 (82.1)	103 (85.1)	300 (83.1)

Characteristic	Nivolumab (n=240)	IC (n=121)	Total (N=361)
Race, n (%)			
White	196 (81.7)	104 (86.0)	300 (83.1)
Black or African American	10 (4.2)	3 (2.5)	13 (3.6)
Asian	29 (12.1)	14 (11.6)	43 (11.9)
Other	5 (2.1)	0	5 (1.4)
Region, n (%)			
North America	101 (42.1)	44 (36.4)	145 (40.2)
Europe	109 (45.4)	62 (51.2)	171 (47.4)
United Kingdom	-	-	34 (9.4)
Rest of the world	30 (12.5)	15 (12.4)	45 (12.5)
Tobacco use, n (%)			
Never	39 (16.3)	31 (25.6)	70 (19.4)
Former/current	191 (79.6)	85 (70.2)	276 (76.5)
Unknown	10 (4.2)	5 (4.1)	15 (4.2)
Disease characteristics			
ECOG PS (%)			
0	49 (20.4)	23 (19.0)	72 (19.9)
1	189 (78.8)	94 (77.7)	283 (78.4)
≥ 2	1 (0.4)	3 (2.5)	4 (1.1)
Not reported	1 (0.4)	1 (0.8)	2 (0.6)
Site of primary tumour, n (%)[a]			
Oral cavity	108 (45.0)	67 (55.4)	175 (48.5)
Pharynx	92 (38.3)	36 (29.8)	128 (35.5)
Larynx	34 (14.2)	15 (12.4)	49 (13.6)
Other	6 (2.5)	3 (2.5)	9 (2.5)
HPV-16 status, n (%)			
Positive	63 (26.3)	29 (24.0)	92 (25.5)
Negative	50 (20.8)	36 (29.8)	86 (23.8)
Not tested[b]	127 (52.9)	56 (46.3)	183 (50.7)
PD-L1 expression, n (%)			
PD-L1 quantifiable	161 (67.1)	99 (81.8)	260 (72.0)
≥1%[c]	88 (54.7)	61 (61.6)	149 (57.3)
<1%[c]	73 (45.3)	38 (38.4)	111 (42.7)
PD-L1 not evaluable	79 (32.9)	22 (18.2)	101 (28.0)
Time from initial diagnosis, median years (range)	2.1 (0.2–17.5)	1.5 (0.1–19.9)	1.9 (0.1–19.9)
Number of disease sites per patient, n (%)			
1	78 (32.5)	42 (34.7)	120 (33.2)
2	82 (34.2)	31 (25.6)	113 (31.3)

Characteristic	Nivolumab (n=240)	IC (n=121)	Total (N=361)
3	60 (25.0)	32 (26.4)	92 (25.5)
4	17 (7.1)	10 (8.3)	27 (7.5)
≥5	2 (0.8)	5 (4.1)	7 (1.9)
Prior therapy			
Number of lines of prior systemic cancer therapy, n (%)			
1	106 (44.2)	58 (47.9)	164 (45.4)
2	80 (33.3)	45 (37.2)	125 (34.6)
≥3	54 (22.5)	18 (14.9)	72 (19.9)
Prior systemic therapy regimen setting, n (%)			
Adjuvant	37 (15.4)	21 (17.4)	58 (16.1)
Neo-adjuvant	17 (7.1)	16 (13.2)	33 (9.1)
Primary	173 (72.1)	83 (68.6)	256 (70.9)
Metastatic disease	112 (46.7)	59 (48.8)	171 (47.4)
Prior surgery related to cancer, n (%)	207 (86.3)	109 (90.1)	316 (87.5)
Prior radiotherapy, n (%)	216 (90.0)	114 (94.2)	330 (91.4)
Prior cetuximab (Case Report Form source), n (%)	150 (62.5)	72 (59.5)	222 (61.5)

[a] Each was not subcategorised to capture a more precise primary tumour site (e.g. oropharynx)
[b] Baseline 'unknown' HPV-p16 status included 180 patients who were not tested (per protocol, HPV-p16 status testing was only required for patients with oropharyngeal disease), 2 patients whose sample was collected after baseline, and 1 nivolumab patient who was tested for HPV-p16, but had a non-evaluable test result.
[c] Percentage presented is for the PD-L1 quantifiable population (PD-L1 database lock of 3rd February 2016).
[d] The percentage of patients with zero prior therapies for metastatic disease cannot necessarily be interpreted as the percentage of first-line patients in this study, as some patients may have received first-line therapy for non-metastatic disease, which was not amenable to surgery and/or radiation.

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; HPV: human papillomavirus; IC: investigator's choice; PD-L1: programmed death ligand 1.
Source: Gillison *et al.* (2016)[8], Ferris *et al.* (2016)[9] and CheckMate 141 CSR (7th June 2016) – Table 5.3.1-1, Table 5.3.1-2 and Table 5.3.2.2-1[14]

4.6 Quality assessment of the relevant randomised controlled trials

An appraisal of CheckMate 141 was performed using the quality assessment tool based on the CRD's guidance for undertaking reviews in health care, as recommended by NICE.[71] The results of the quality assessment for CheckMate 141 are presented in Table 14.

In summary, CheckMate 141 can be considered to be a high-quality and well-conducted RCT. However, bias may have been introduced in the trial due to its open-label design, which meant that patients and study investigators were not blinded to study treatment. However, given the nature of OS (time to death) as an objective measure, the analysis of the primary endpoint in CheckMate 141 is considered to be less susceptible to detection bias than other more subjective measures.

Table 14: Quality assessment results for CheckMate 141

	CheckMate 141	
	Response	**Justification for response**
Was randomisation carried out appropriately?	Yes	Randomisation was conducted using a centralised IVRS
Was the concealment of treatment allocation adequate?	No	The intended IC of therapy was entered in the IVRS for all patients prior to randomisation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline demographics and disease characteristics were generally well-balanced between treatment groups (see Section 4.5)
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	CheckMate 141 was an open-label study
Were there any unexpected imbalances in drop‑outs between groups?	No	A higher proportion of patients in the IC arm (97.3%) did not continue with study treatment compared to the nivolumab arm (82.6%). However, the majority of discontinuations were due to disease progression (70.6%) or study drug toxicity (5.8%), which were both greater in the IC arm (see Section 4.5), and are both expected reasons for discontinuation. A higher proportion of randomised patients did not receive treatment in the IC arm (8.3%) than the nivolumab arm (1.7%). Given that the main reason for randomised patients in the IC arm not receiving study treatment was withdrawal of consent, this may reflect the open-label nature of the trial and the fact that patients did not want to proceed with the trial upon finding they had been randomised to IC of therapy.

Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All primary and secondary endpoints listed have been reported in the CSR (7th June 2016)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Analyses of efficacy outcomes, including the primary endpoint, were conducted in the all-randomised population. For time to event outcomes, appropriate censoring methods were used (see Section 4.4).

Adapted from Systematic reviews: CRD's guidance for the undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[61]
These results were based on an appraisal of CheckMate 141 using the CheckMate 141 CSR (7th June 2016)[14]

Abbreviations: CRD: Centre for Reviews and Dissemination; CSR: Clinical Study Report; IC: investigator's choice; IVRS: interactive voice response system.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Summary of the clinical effectiveness results – CheckMate 141

- Nivolumab demonstrated significant improvements in OS relative to IC of therapy (HR 0.70 [97.73% CI, 0.51 to 0.96; p=0.0101]), corresponding to a 30% reduction in the risk of death with nivolumab versus IC of therapy
  - Median OS was prolonged in the nivolumab arm (7.5 months; 95% CI, 5.5 to 9.1) compared to IC (5.1 months; 95% CI, 4.0 to 6.0)
  - 1-year survival was more than doubled in the nivolumab arm (36.0%) versus IC of therapy (16.6%)
- Median PFS was similar between treatment arms; however, a delayed separation of Kaplan-Meier curves in favour of nivolumab was observed (HR, 0.89; 95% CI, 0.70, 1.1; p=0.3236)
- ORR was more than doubled in the nivolumab arm (13.3%; 95% CI, 9.3, 18.3) compared to the IC arm (5.8%; 95% CI, 2.4, 11.6)

Patient-reported HRQoL outcomes

- Patient-reported outcomes were evaluated using the EORTC QLQ-C30 and head-and-neck-specific module (QLQ-H&N35), with clinically meaningful changes defined as a change from baseline of ≥10 points. Health problems and perceived health status were also assessed using the EQ-5D-3L
- Patients in the IC arm reported meaningful worsening in scores for numerous scales of the EORTC QLQ-C30 (e.g. physical, emotional, and social functioning; fatigue; dyspnoea) and QLQ-H&N35 (e.g. pain, sensory problems, trouble with social contact, sticky saliva, nutritional supplement use), while HRQoL in the nivolumab arm was generally stable with patients exhibiting no meaningful changes across the majority of EORTC QLQ-C30 and QLQ-H&N35 scales in the first 21 weeks of follow-up
  - Significant differences between treatment arms at both Weeks 9 and 15 in favour of nivolumab versus IC of therapy were observed for physical functioning, role functioning, social functioning, fatigue, dyspnoea and appetite loss (EORTC QLQ-C30), and pain and sensory problems (EORTC QLQ-H&N35) ($p<0.05$)
- Health problems were more prevalent in the IC arm than the nivolumab arm as measured by the EQ-5D-3L

Overview of clinical effectiveness results

An overview of clinical effectiveness results from CheckMate 141 for nivolumab and the total IC arm is presented in Table 15. Full results for primary, secondary and exploratory clinical endpoints are presented in the subsequent sections. As discussed in Section 4.4, the main clinical effectiveness results presented in this submission are for nivolumab versus the total IC comparator arm, reflecting the two randomisation groups of the CheckMate 141 trial. An exploratory subgroup analysis of OS by intended therapy for the IC arm is presented in Section 4.8.

Table 15: Overview of clinical effectiveness results from CheckMate 141 – all-randomised population

Outcome[a]	Nivolumab (n=240)	IC (n=121)
Overall Survival		
Deaths, n (%)	133 (55.4)	85 (70.2)
Median OS, months (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
HR for death with nivolumab (97.73% CI; p-value)[b]	0.70 (0.51, 0.96; p=0.0101)	
1-year survival rate, % (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)
Progression-free survival[c]		
Events, n (%)	190 (79.2)	103 (85.1)
Median PFS, months (95% CI)	2.0 (1.9, 2.1)	2.3 (1.9, 3.1)
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)	
6-month PFS rate, % (95% CI)	19.7 (14.6, 25.4)	9.9 (5.0, 16.9)
Tumour response[c]		
ORR, n (%) [95% CI]	32 (13.3) [9.3, 18.3]	7 (5.8) [2.4, 11.6]
Median TTR, months (range)	2.1 (1.8–7.4)	2.0 (1.9–4.6)

[a] Results are presented from the initial database lock of 18th December 2015 for OS and from the database lock of 5th May 2016 for PFS and tumour response.
[b] The pre-specified boundary for statistical significance required the p-value to be less than 0.0227; 95% CI were 0.53, 0.92
[c] Disease progression and tumour response were assessed by the investigator using RECIST version 1.1

Abbreviations: CI: confidence intervals; HR: hazard ratio; IVRS: interactive voice response system; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumours; TTR: time to response.
Source: Gillison *et al.* (2016),[8] Ferris *et al.* (2016)[9] and CheckMate 141 CSR (7th June 2016)[14]

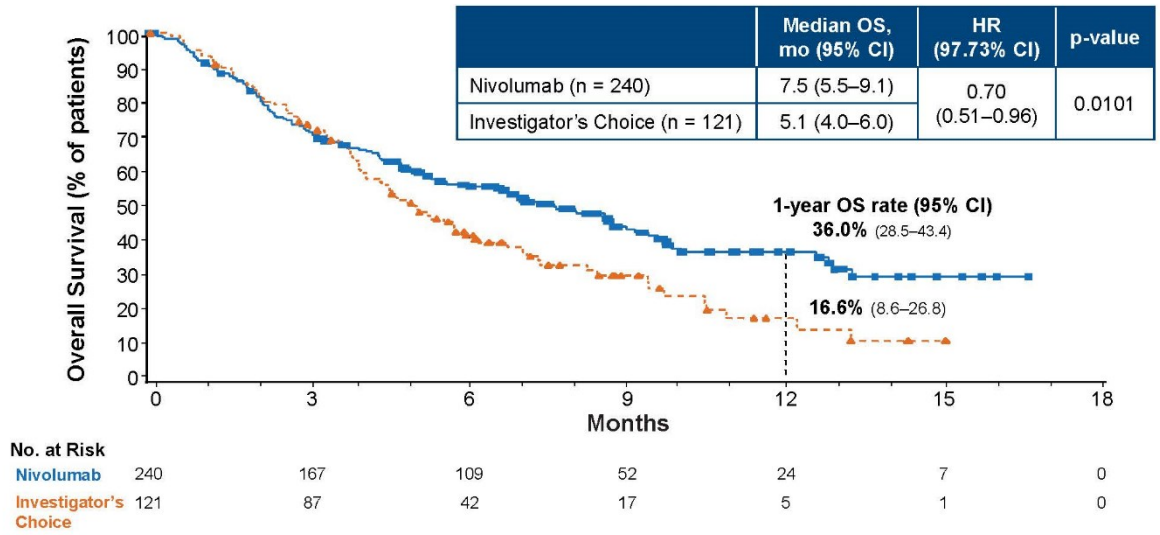
4.7.1 Primary efficacy results in CheckMate 141

CheckMate 141 met the primary endpoint, with significant improvements in OS demonstrated in the nivolumab arm compared to the IC arm (HR, 0.70 [97.73% CI, 0.51, 0.96]; stratified log-rank test p-value = 0.0101), equivalent to a 30% reduction in risk of death with nivolumab versus IC of therapy.[8]

At the time of the initial database lock (18th December 2015), median OS was higher in the nivolumab arm (7.5 months; 95% CI, 5.5, 9.1) versus the IC arm (5.1 months; 95% CI 4.0, 6.0), after a median follow-up of 5.3 months (range, 0–16.8) and 4.6 months (range, 0.0–15.2) for each treatment group, respectively.[8] Such improvements in OS are supported by survival rates at 12 months, which were more than doubled in the nivolumab arm (36.0%) compared to the IC arm (16.6%).[8] At the time of the database lock, deaths had occurred in a total of 218 patients (60.4%), of which 133 patients were randomised to the nivolumab arm (55.4%) and 85 patients to the IC arm (70.2%).[8]

The Kaplan-Meier plot for OS is presented in Figure 10.

Figure 10: Kaplan-Meier plot for overall survival in the all-randomised population in CheckMate 141



The pre-specified boundary for statistical significance required the p-value to be less than 0.0227; 95% CI were 0.53, 0.92. The HR was computed using a stratified Cox proportional hazards model and the p-value was from a stratified log-rank test.
Database lock of 18th December 2015.

Abbreviations: CI: confidence intervals; HR: hazard ratio; OS: overall survival.
Source: Gillison *et al.* (2016)[8]

Reduced hazard rates for death relative to IC were observed across various relevant subgroups (see Section 4.8), suggesting that nivolumab is effective versus IC regardless of HPV-p16 status, the level of PD-L1 expression (≥1% or <1%) and other baseline characteristics.

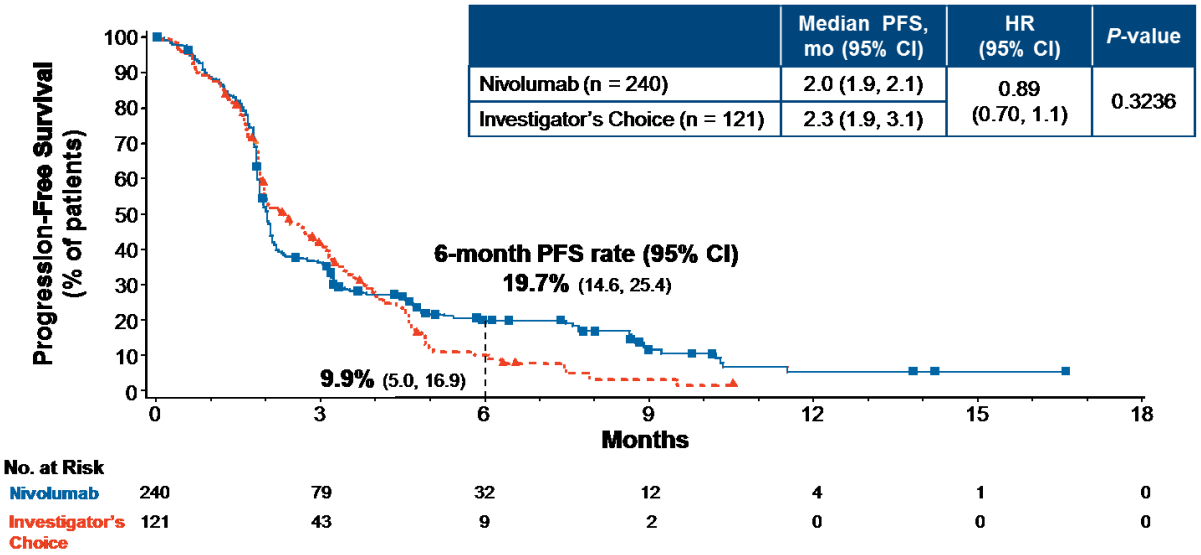
4.7.2 Secondary efficacy results in CheckMate 141

Progression-free survival

Although median PFS was less prolonged in the nivolumab arm (2.0 months [95% CI, 1.9, 2.1] for nivolumab versus 2.3 months [95% CI, 1.9, 3.1] for IC of therapy), the overall HR for disease progression or death favoured nivolumab (HR, 0.89; 95% CI, 0.70, 1.1; p=0.3236) (based on events up to the database lock of 18th December 2015).[9] As shown in Figure 11, there was delayed separation of the Kaplan-Meier curves in favour of nivolumab and by 6 months the PFS rate was higher in the nivolumab arm (19.7% [95% CI, 14.6, 25.4]) compared to the IC arm (9.9% [95% CI, 5.0, 16.9]).[9] A delayed separation of curves is consistent with other trials of nivolumab versus chemotherapy in other cancer indications and may be reflective of the mechanism of action of nivolumab as an immune-checkpoint inhibitor, as described in Section 2.1, and the resultant potential limitations of the RECIST criteria as a measure of true progression with immune-checkpoint inhibitors (see Section 4.3.3).[19, 20]

The number of patients that had experienced a PFS event by the time of the database lock was 190 (79.2%) in the nivolumab arm and 103 (85.1%) in the IC arm.[14] In total, 139 and 71 patients in the nivolumab and IC arms, respectively, had experienced disease progression, assessed using RECIST version 1.1, as the PFS-defining event, and 51 and 32 patients in each arm had died prior to experiencing disease progression.[14]

Figure 11: Kaplan-Meier plot for progression-free survival in the all-randomised population in CheckMate 141



Disease progression was assessed by the investigator using RECIST version 1.1. The HR was computed using a stratified Cox proportional hazards model and the p-value was from a stratified log-rank test.
Since death information was not updated for the latest database lock, and since PFS depends on both progression and death, PFS analyses were restricted to progression events (deaths or radiographic progressions) prior to the initial database lock of 18th December 2015.

Abbreviations: CI: confidence intervals; HR: hazard ratio; PFS: progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Ferris *et al.* (2016)[9]

Tumour response – ORR and Time to Response (TTR)

The ORR was greater for nivolumab versus IC of therapy (13.3% versus 5.8%), with a higher proportion of patients in the nivolumab arm achieving a best overall response of either a complete or partial response, as compared to the IC arm (see Table 16).[9] The median TTR was similar in both treatment arms (2.1 months [range, 1.8–7.4] with nivolumab versus 2.0 months [range, 1.9–4.6] with IC of therapy]); however, as shown in Figure 12, nivolumab may offer a more durable response compared to IC of therapy, with responses maintained beyond 40 weeks for some patients in the nivolumab arm.[9]

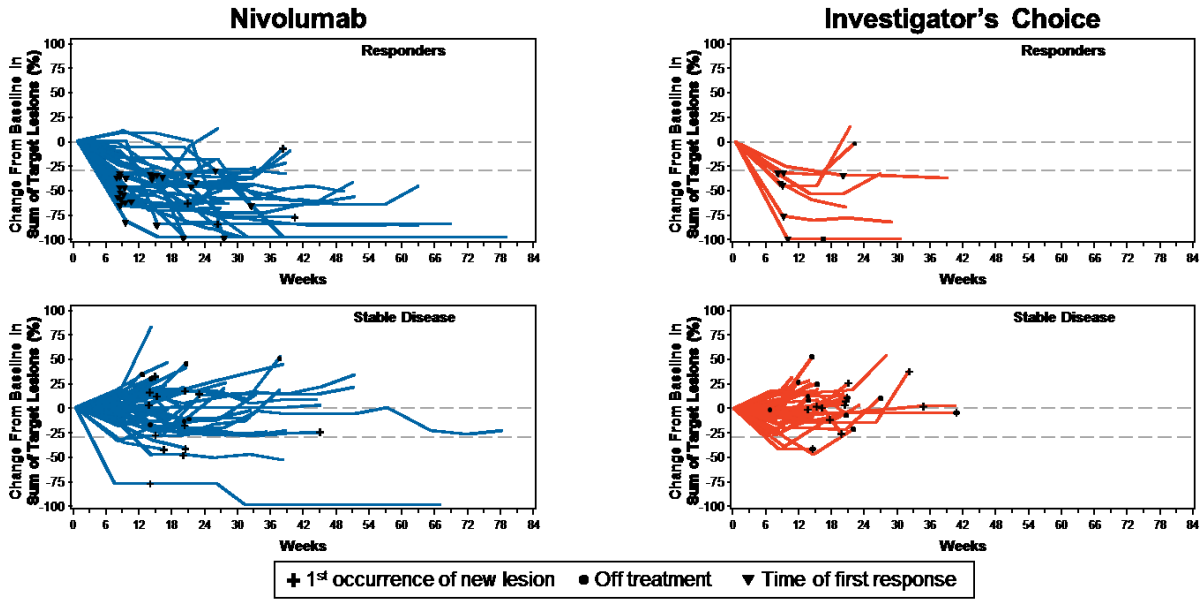
Table 16: Response to treatment in the all-randomised population in CheckMate 141

Tumour response	Nivolumab (n=240)	IC (n=121)
Best overall response, n (%)		
Complete response	6 (2.5)	1 (0.8)
Partial response	26 (10.8)	6 (5.0)
Stable disease	55 (22.9)	43 (35.5)
Progressive disease	100 (41.7)	42 (34.7)
Not determined	53 (22.1)	29 (24.0)
Objective response rate, n (%)	32 (13.3)	7 (5.8)
95% CI	9.3, 18.3	2.4, 11.6
Median TTR, months (range)	2.1 (1.8–7.4)	2.0 (1.9–4.6)

Response was assessed by the investigator using RECIST version 1.1.
Database lock of 5th May 2016.

Abbreviations: CI: confidence intervals; DOR: duration of response; IC: investigator's choice; RECIST: Response Evaluation Criteria In Solid Tumours; TTR: time to response.
Source: Ferris *et al.* (2016)[9]

Figure 12: Change in tumour burden over time in the all-randomised population in CheckMate 141



Lines represent tumour burden for individual patients with changes in the y-axis representing changes from baseline in the sum of target lesions over time. Tumour burden is characterised for patients who achieved a response (top panel), as assessed by the investigator using RECIST version 1.1, and those with stable disease (bottom panel). Time to response, time to the first occurrence of a new lesion and time to treatment withdrawal are presented.
Database lock of 5th May 2016.

Abbreviation: RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Ferris *et al.* (2016)[9]

Treatment beyond progression

As of the database lock of 5th May 2016, a total of 58/236 (24.6%) of patients in the nivolumab arm continued treatment beyond RECIST-defined progression, as permitted by the study protocol (see Section 4.3.1); the majority of these patients (n=43) had achieved a best overall response of either a complete or partial response prior to initial RECIST-defined progression.[14]

The 15 patients who continued treatment and had not achieved either a complete or partial response, met at least one of the following criteria:

- Appearance of a new lesion followed by decrease from baseline of at least 10% in the sum of the target lesions (n=2)
- Initial increase from nadir of at least 20% in the sum of the target lesions followed by at least two tumour assessments showing no further progression defined as a 10% additional increase in sum of target lesions and new lesions (n=13)[14]

These patients could be described as experiencing an "unconventional immune-related response," as described in Section 2.1.

Patient-reported HRQoL outcomes: EORTC QLQ-C30 and EORTC QLQ-H&N35

At baseline, completion rates were 79.6% (191/240) and 80.4% (193/240) in the nivolumab arm, for EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires, respectively, and 75.2% (91/121) (for both instruments) in the IC arm.[14] Completion rates, calculated as a percentage of patients on study, met or exceeded 70% at all save two assessments (Weeks 15 and 39) through the first 45 weeks of follow up in the nivolumab arm (both instruments). After this time-point, fewer than 10 patients were eligible for on-study assessment of patient-reported HRQoL outcomes.[14] In the IC arm, on-study completion rates declined rapidly from baseline falling to 50.0% of patients on study by Week 21 for EORTC QLQ-C30 and Week 15 for EORTC QLQ-H&N35.[14] After Week 21, fewer than 10 patients in the IC arm were eligible for on-treatment assessment using either instrument.[14] As such, results have been presented up to Week 21 for nivolumab and IC of therapy to allow comparison between the two treatment arms.

EORTC QLQ-C30

As detailed in Section 4.4, the EORTC QLQ-C30 is a 30-item questionnaire composed of both multi-item scales (physical, role, emotional, social and cognitive – functional scales; fatigue, nausea and vomiting, and pain – symptom scales; and a global health status/HRQoL scale) and single-item measures (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). Raw scores for the EORTC QLQ-C30 are transformed to a 0–100 scale with higher scale scores representing better functioning or HRQoL (functional and global health status/HRQoL scales) or worsening of symptoms (symptom scales). A clinically meaningful change in score was regarded as a change in ≥10 points.[68]

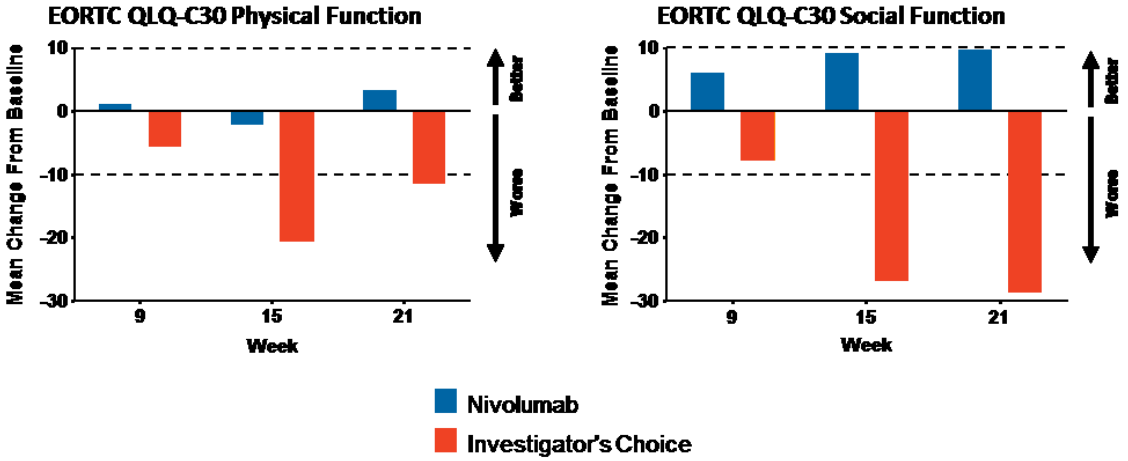
At baseline, there were no meaningful differences in EORTC QLQ-C30 scale scores between the nivolumab and IC arms.[14] Over the first 21 weeks of follow up, no meaningful deteriorations in scale scores from baseline were reported for patients assigned to nivolumab, suggesting that patient HRQoL and symptom control was generally stabilised with nivolumab.[14] Conversely, those assigned to the IC arm exhibited meaningful worsening (≥10 points) in many functional domains and symptoms, predominantly at Weeks 15 and 21, including physical, role, emotional, cognitive, and social function; fatigue; nausea and vomiting; dyspnoea; insomnia; diarrhoea, and appetite loss.[14] The IC arm did however exhibit a meaningful improvement in constipation at Week 15 (mean change, -17.9 points), though similar improvements were not observed at Weeks 9 and 21.[14]

Significant differences between treatment arms were observed in favour of nivolumab at both Weeks 9 and 15 compared to the IC arm for physical functioning, role functioning, social functioning, fatigue, dyspnoea and appetite loss ($p<0.05$; ANCOVA adjusted for prior cetuximab

therapy and baseline score included as a covariate).[22] Moreover, time to deterioration was significantly delayed for nivolumab versus IC for global health, physical functioning, role functioning, cognitive functioning, social functioning, fatigue, dyspnoea and insomnia (p<0.05; Cox proportional hazards model with prior cetuximab therapy and baseline score as covariates; deterioration was defined as a meaningful worsening of 10 points).[22]

Figures included in the published congress presentation by Ferris *et al.* (2016)[9] are presented in Figure 13 for physical function and social function – two relevant functional domains for patients with R/M SCCHN.

Figure 13: EORTC QLQ-C30 mean changes from baseline – physical function and social function



Raw scores for the EORTC QLQ-C30 were transformed to a 0–100 scale with higher scale scores representing better functioning. A clinically meaningful change in score was regarded as a change in ≥10 points.[68]

Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30.
Source: Ferris *et al.* (2016)[9]

EORTC QLQ-H&N35

The EORTC QLQ-H&N35 is a validated 35-item measure of concerns and symptoms specific to patients with cancer of the head and neck.[49] As with the EORTC QLQ-C30, raw scores from the EORTC QLQ-H&N35 are transformed to a 0–100 scale with higher values indicating worsening of symptoms. A clinically meaningful change in score was regarded as a change in ≥10 points.[21]

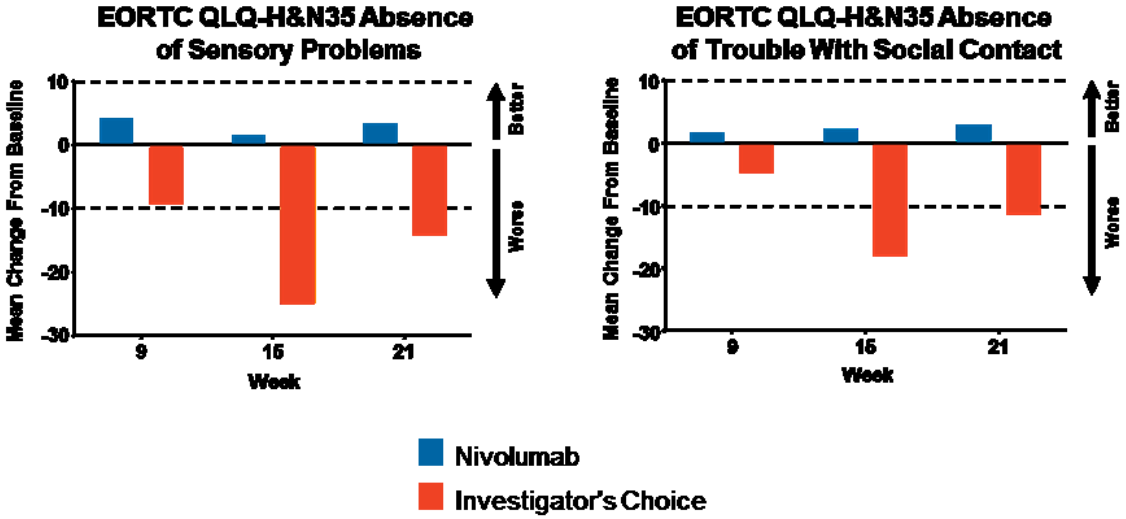
At baseline, there were no meaningful differences in EORTC QLQ-H&N35 scale scores between the nivolumab and IC arms.[14] With the exception of dry mouth at Week 21 (mean change, 12.5 points), patients assigned to nivolumab did not exhibit meaningful worsening in symptoms or concerns relative to baseline up to Week 21.[14] In contrast, meaningful increases in scores from baseline indicative of symptom worsening were reported over the first 21 weeks in the IC arm for numerous domains, including pain, sensory problems, social contact, loss of sexuality, teeth problems, sticky saliva, feeling ill and nutritional supplement use.[14]

Significant differences between treatment arms were observed in favour of nivolumab at both Weeks 9 and 15 compared to the IC arm for pain and sensory problems (p<0.05; ANCOVA adjusted for prior cetuximab therapy and baseline score included as a covariate).[22] Moreover, time to deterioration was significantly delayed for nivolumab versus IC for pain, sensory problems and opening mouth (p<0.05; Cox proportional hazards model with prior cetuximab therapy and

baseline score as covariates; deterioration was defined as a meaningful worsening of 10 points).[22]

Figures included in the published congress presentation by Ferris *et al.* (2016)[9] are presented in Figure 14 for the absence of sensory problems and the absence of trouble with social contact – two relevant symptoms/concerns for patients with R/M SCCHN.

Figure 14: EORTC QLQ-H&N35 mean changes from baseline – absence of sensory problems and absence of trouble with social contact



Raw scores for the EORTC QLQ-H&N35 were transformed to a 0–100 scale. Where the absence of each item is considered, higher scale scores represent improvements in symptoms. A clinically meaningful change in score was regarded as a change in ≥10 points.[21]

Abbreviations: EORTC QLQ-H&N35: European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Head and Neck 35.
Source: Ferris *et al.* (2016)[9]

Patient-reported HRQoL outcomes: EQ-5D[67]

EQ-5D-3L questionnaire responses were collected as part of CheckMate 141 with attribute-specific completion rates at baseline ranging from [redacted]% (usual activities) to [redacted]% (mobility) in the nivolumab arm and [redacted]% (pain/discomfort) to [redacted]% (mobility and self-care) in the IC arm.[14] During the first 21 weeks of follow-up, health problems were more prevalent in the IC arm relative to nivolumab, with a >10% difference in the percentage of patients reporting health problems for self-care at Week 9; for mobility, self-care, pain/discomfort, and anxiety/depression at Week 15; and for mobility, usual activities, and pain/discomfort at Week 21.[14] Responses to the EQ-5D-3L were subsequently converted to EQ-5D utility values using the UK-specific scoring algorithm published by Dolan *et al.* (1997).[22, 72] The utility values obtained from these responses are presented in Section 5.4.1 as part of the economic analysis of nivolumab versus comparators.

4.8 Subgroup analysis

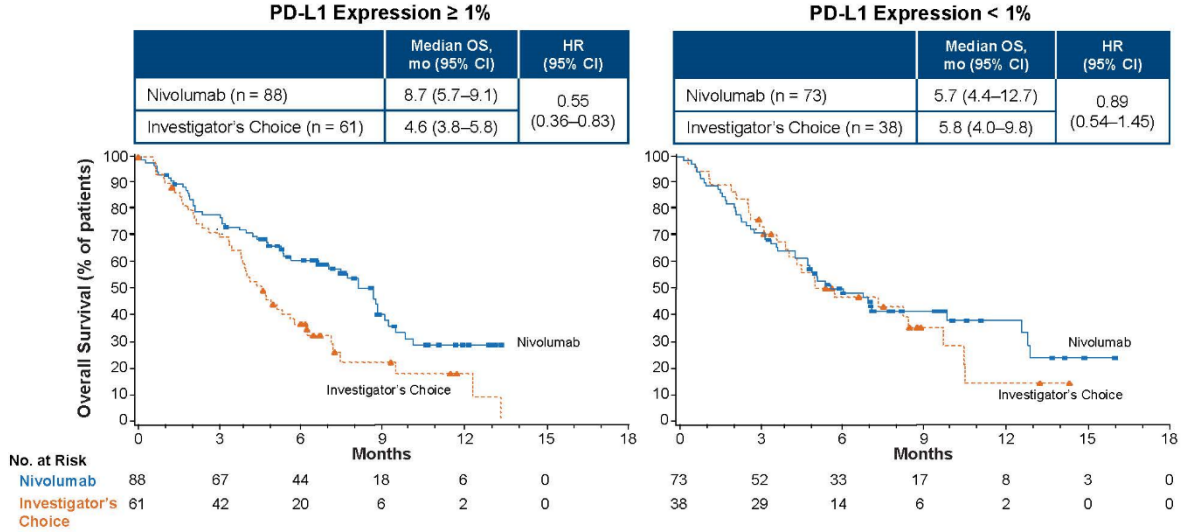
Exploratory subgroup analyses conducted in CheckMate 141 included OS by treatment group and:

- PD-L1 expression (≥1% or <1%)
- HPV-p16 status (positive or negative)
- Selected baseline characteristics, including age (<65 or ≥65 to <75 or ≥75), Eastern Cooperative Oncology Group (ECOG) performance status (0 or ≥1), tobacco use (current/former or never), prior lines of systemic therapy (1 or 2 or ≥3) and by intended choice of therapy for the IC arm (docetaxel, methotrexate or cetuximab)

Across all of these subgroups, nivolumab demonstrated reductions in the hazard rate of death versus IC, regardless of PD-L1 expression (see Figure 15), HPV-p16 status (see Figure 16) and selected baseline characteristics (see Figure 17), including intended therapy for the IC arm. Notably, with regards to PD-L1 expression, no further benefit in OS was reported at increasing levels of PD-L1 expression (≥5% and ≥10%).[9]

Overall, these results demonstrate that the improved efficacy of nivolumab versus IC of therapy is generalisable across all relevant subgroups of patients included in the CheckMate 141 trial.

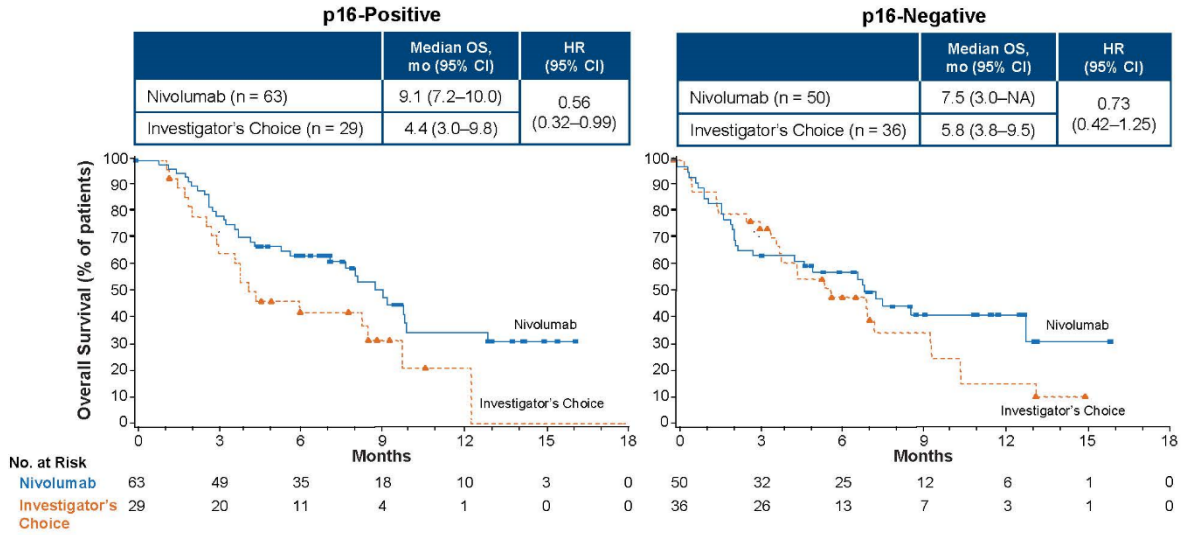
Figure 15: Kaplan-Meier plots for overall survival by PD-L1 expression (≥1% or <1%) in the PD-L1 quantifiable population in CheckMate 141



Database lock of 3rd February 2016.

Abbreviations: CI: confidence intervals; HR: hazard ratio; OS: overall survival; PD-L1: programmed death ligand 1.
Source: Gillison *et al.* (2016)[8]

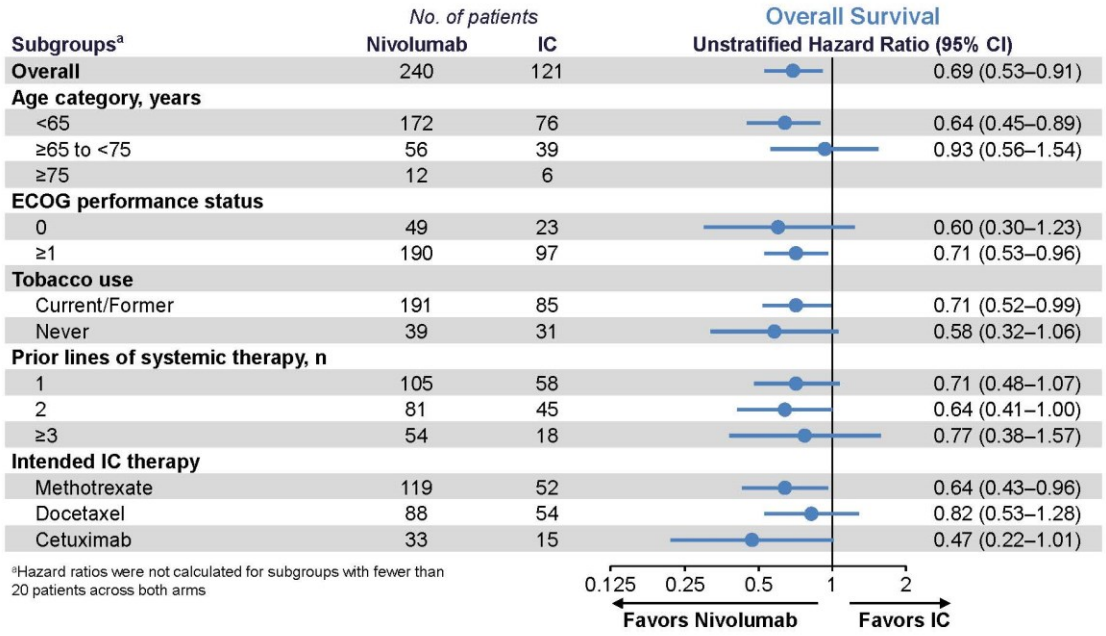
Figure 16: Kaplan-Meier plots for overall survival by p16 status (positive or negative) in patients with documented p16 status at baseline in CheckMate 141



Database lock of 18th December 2015.

Abbreviations: CI: confidence intervals; HR: hazard ratio; OS: overall survival.
Source: Gillison *et al.* (2016)[8]

Figure 17: Kaplan-Meier plots for overall survival by selected baseline characteristics, including intended IC therapy, in CheckMate 141



Database lock of 18th December 2015.

Abbreviations: CI: confidence intervals; ECOG: Eastern Cooperative Oncology Group; IC: investigator's choice; OS: overall survival.
Source: Gillison *et al.* (2016)[8]

4.9 Meta-analysis

As noted in Section 4.2, CheckMate 141 was the only trial identified in the SLR that was relevant to the decision problem. As such, no meta-analysis has been conducted.

Clinical effectiveness results from the CheckMate 141 are presented in Section 4.7.

4.10 Indirect and mixed treatment comparisons

The relevant comparators to nivolumab in this submission are docetaxel, methotrexate and paclitaxel (see Section 1.1). Evidence for the efficacy of nivolumab versus docetaxel and methotrexate is available from the CheckMate 141 trial presented in Section 4.7, in which docetaxel and methotrexate comprised the main therapies in the IC arm with which nivolumab was directly compared. The clinical SLR identified no further clinical evidence for nivolumab versus docetaxel or methotrexate in the relevant indication (see Section 4.1).

As noted in Section 3.2, clinical expert opinion suggests that there is no difference in efficacy in terms of OS between the comparators listed in the final scope for this appraisal (docetaxel, paclitaxel and methotrexate).[6, 7] Data from a phase II clinical trial of docetaxel versus methotrexate in recurrent SCCHN (albeit not specifically platinum-refractory, and hence not included in the SLR) provides supportive evidence for this, indicating no difference in survival with these therapies.[58] No further studies providing data on the relative efficacy of docetaxel, methotrexate and paclitaxel versus one another or nivolumab were identified in the clinical SLR, as shown below.

ITT results from the IC arm of CheckMate 141 are therefore considered applicable to all three comparators included in this appraisal.[6] Moreover, given that results from the SLR indicate that there is insufficient clinical trial data that could be used to make relevant, indirect comparisons between the therapies included as comparators in the scope for this appraisal (see Section 4.1 and below), an indirect treatment comparison was not considered appropriate for this submission.

Relevant randomised controlled trials identified in the clinical SLR for comparators

A review of the 118 ultimately included publications from both the original and the updated SLRs (see Section 4.1) was performed to identify any studies reporting data on the efficacy and safety of the relevant comparators in this submission (docetaxel, methotrexate and paclitaxel), which could allow for a potential indirect comparison with nivolumab. Studies reporting data on the efficacy and safety of cetuximab were also included within this review, since this intervention was also part of the IC arm of the CheckMate 141 trial. Therefore, despite the fact that cetuximab is not considered a relevant comparator to nivolumab in this submission as it is not used in UK clinical practice, data on the efficacy and safety of cetuximab could potentially be used in an indirect comparison with nivolumab.

Details of the studies included in the SLR that provided data on the efficacy and safety of any of the relevant appraisal comparators or cetuximab are presented in Table 17 below. As can be seen from the below list, no randomised trials (in addition to CheckMate 141) in patients with platinum-refractory R/M SCCHN were identified in the SLR that investigated the use of comparators included in this appraisal versus one another or nivolumab or a common comparator therapy. As such, an indirect comparison between nivolumab and the therapies included as comparators for this appraisal was not considered appropriate for this submission.

Table 17: Relevant publications identified in the clinical systematic literature review for comparators

No.	Trial	Trial design	Population	Intervention	Comparator(s)	Primary study reference; *Secondary study reference(s)*
1	Limaye (2013)	Phase II, open-label, randomised, multicentre study	Patients with R/M SCCHN who had progressed after platinum-based therapy	Docetaxel (i.v. 75 mg/m^2 every 3 weeks); n=14	Docetaxel (i.v. 75 mg/m^2 every 3 weeks) plus vandetanib (oral 100 mg daily); n=15	Limaye (2013)[73]
2	Seiwert (2014)	Phase II, open-label, randomised, multicentre study	Patients with R/M SCCHN who had progressed after platinum-based therapy	Cetuximab (i.v. 250 mg/m^2 per week); n=60	Afatinib (oral 50 mg daily); n=61	Seiwert (2014);[74] *Seiwert (2012),[75] Cupissol (2013),[76] Seiwert (2010a),[77] Cohen (2012),[78] Seiwert (2010b)[79]*
3	Kushwaha (2015)	Open-label, randomised study	Patients with recurrent SCCHN (80% had prior platinum therapy)	Methotrexate (i.v. 40 mg/m^2) once weekly; n=40	Gefitinib (oral 500 mg daily); n=39 Methotrexate (i.v. 40 mg/m^2) plus 5-fluorouracil (i.v. 600 mg/m^2) weekly; n=38	Kushwaha (2015)[80]
4	Rottey (2015)	Phase II, randomised study	Patients with recurrent SCCHN and progressive disease within 1 year of platinum-therapy	Methotrexate (i.v. 40 mg/m^2 once weekly); n=48	Cabazitaxel (i.v. 20 mg/m^2 every 3 weeks increased to 25 mg/m^2 for subsequent cycles if no adverse events); n=53	Rottey (2015)[81]
5	Jimeno (2015a)	Phase II, open-label, randomised study	Patients with R/M SCCHN who had received at least one prior platinum-based therapy	Docetaxel (i.v. 75 mg/m^2 every 3 weeks); n=43	Docetaxel (i.v. 75 mg/m^2 every 3 weeks) plus PX-866 (oral 8 mg daily); n=42	Jimeno (2015a)[82]
6	LUX-Head and Neck-1	Phase III, open-label, randomised study	Patients with R/M SCCHN who had progressed after first-line platinum therapy	Methotrexate (i.v. 40 mg/m^2 once weekly); n=161	Afatinib (oral 40 mg/day); n=322	Machiels (2015);[83] *Machiels (2012),[84] Cohen (2015),[85] Machiels (2014),[86] Clement (2015),[87]*

						Clement (2016),[88] Cohen (2016),[89] Tahara (2015)[90]
7	Jimeno (2015b)	Phase II, randomised study	Patients with R/M SCCHN who had received at least one prior platinum-based therapy	Cetuximab (i.v. 400 mg/m^2 loading dose followed by i.v. 250 mg/m^2 weekly); n=41	Cetuximab (i.v. 400 mg/m^2 loading dose followed by i.v. 250 mg/m^2 weekly) plus PX-866 (oral 8 mg daily); n=42	Jimeno (2015b)[91]
8	Vokes (2015)	Phase II, randomised study	Patients with R/M SCCHN after platinum failure	Cetuximab (i.v. 500 mg/m^2 every 2 weeks); n=38	Cetuximab (i.v. 500 mg/m^2 every 2 weeks) plus tivantinib (oral 360 mg twice daily); n=40	Vokes (2015)[92]
9	Stewart (2009a)	Phase III, randomised study	Patients with recurrent SCCHN after radical radiation therapy (with or without concomitant platinum-based therapy)	Methotrexate (i.v. 40 mg/m^2 once weekly); n=161	Gefitinib (oral 250 mg daily); n=158 Gefitinib (oral 500 mg daily); n=167	Stewart (2009a);[93] *Stewart (2009b)[94]*
10	Fayette (2014)	Phase II, open-label, randomised, multicentre study	Patients with R/M SCCHN who had progressed after platinum-based therapy	Cetuximab (i.v. 400 mg/m^2 loading dose followed by i.v. 250 mg/m^2 weekly); n=62	MEHD7945A (i.v. 1100 mg every 2 weeks); n=59	Fayette (2014)[95]
11	BERIL-1	Phase II, randomised study	Patients with platinum pre-treated R/M SCCHN	Paclitaxel (i.v. 80 mg/m^2 weekly) plus placebo; n=79	Paclitaxel (i.v. 80 mg/m^2 weekly) plus buparlisib (oral 100mg daily); n=79	Soulieres (2016),[96] *Licitra (2016)[97]*
12	Tahara (2011)	Phase II, single-arm study	Patients with R/M SCCHN and one or no prior chemotherapy regimens	Paclitaxel (i.v. 100 mg/m^2 once weekly for 6 weeks of a 7-week cycle); n=74	N/A	Tahara (2011)[98]
13	Zenda (2007)	Retrospective, single-arm study	Patients with SCCHN and progression/ recurrence after platinum-based therapy	Docetaxel (i.v. 60 mg/m^2 every 3-4 weeks); n=20	N/A	Zenda (2007)[99]
14	Dreyfuss (1996)	Phase II, single-arm study	Patients with SCCHN that was either newly-diagnosed or recurrent	Docetaxel (i.v. 100 mg/m^2 every 3 weeks); n=31	N/A	Dreyfuss (1996)[100]

15	Caballero (2007)	Before-and-after study	Patients with R/M SCCHN refractory to platinum-based therapies	Paclitaxel (i.v. 80 mg/m^2 once weekly for 6 weeks); n=33	N/A	Caballero (2007)[101]
16	Vermorken (2007)	Phase II, open-label study	Patients with R/M SCCHN who have progressed on platinum therapy	Cetuximab (i.v. 400 mg/m^2 loading dose followed by i.v. 250 mg/m^2 weekly); n=62	N/A	Vermorken (2007)[102]
17	Grau (2009a)	Phase II, single-arm study	Patients with platinum-resistant R/M SCCHN	Paclitaxel (i.v. 80 mg/m^2 once weekly for 6 weeks); n=60	N/A	Grau (2009a)[103]
18	Grau (2009b)	Single-arm study	Patients with SCCHN and progression following platinum-based chemotherapy	Paclitaxel (i.v. 80 mg/m^2 once weekly for 6 weeks); n=47	N/A	Grau (2009b)[104]
19	Nash-Smyth (2015)	Retrospective medical record review	Patients with metastatic SCCHN	Third line of therapy: • 40 (18.2%) patients received docetaxel monotherapy • 43 (19.6%) patients received cetuximab monotherapy • 43 (19.6%) patients received methotrexate monotherapy 94 (42.7%) patients received other therapies	N/A	Nash-Smyth (2015)[5]

Abbreviations: i.v.: intravenous; N/A: not applicable; R/M: recurrent or metastatic; SCCHN: squamous-cell carcinoma of the head and neck.

4.11 Non-randomised and non-controlled evidence

No relevant non-randomised or non-controlled evidence for the use of nivolumab as a treatment for adults with R/M SCCHN who have progressed after platinum-based therapy were identified in the SLR (see Section 4.1).

4.12 Adverse reactions

CheckMate 141 safety analysis

- Nivolumab was generally well tolerated by patients in CheckMate 141 compared to IC of therapy:
  - **All-causality Grade 3-4 AEs**: a lower proportion of patients receiving nivolumab experienced Grade 3-4 AEs (41.1% versus 52.3%) and Grade 3-4 SAEs (28.0% versus 32.4%) of any cause compared to the IC arm; Grade 3-4 AEs of any cause leading to discontinuation were similar between treatment arms (11.4% versus 10.8%)
  - **Drug-related Grade 3-4 AEs**: a lower proportion of patients receiving nivolumab experienced drug-related Grade 3-4 AEs (13.1% versus 35.1%), drug-related Grade 3-4 SAEs (4.7% versus 10.8%) and drug-related Grade 3-4 AEs leading to discontinuation (2.5% versus 6.3%)
- Treatment discontinuations due to any grade AE (all causality) were similar between groups (21.6% nivolumab versus 24.3% IC), but proportions were lower in the nivolumab arm compared to IC of therapy (3.8% versus 9.9%) for drug-related AEs of any grade
- The most frequently reported AEs of any cause in the nivolumab arm were (**any grade**): fatigue (26.3%), nausea (19.1%), anaemia (18.6%), decreased appetite (18.6%), malignant neoplasm progression (18.2%), and constipation (15.3%); and (**Grade 3-4**): anaemia (5.9%), dyspnoea (5.5%), hyponatremia (4.7%), dysphagia (3.8%), and pneumonia (3.8%)
- Two deaths were reported in the nivolumab arm that were considered to be related to study drug toxicity (Grade 3 pneumonitis and Grade 5 hypercalcaemia)
- 'Select' AEs did occur in CheckMate 141 but were mostly Grade 1-2 and were generally manageable using the recommended treatment guidelines
- No new safety concerns with nivolumab were identified in CheckMate 141, with a similar safety/tolerability profile observed to that seen in trials of nivolumab monotherapy in other cancer types

The safety and tolerability of nivolumab for patients with platinum-refractory R/M SCCHN was evaluated as part of the phase III RCT, CheckMate 141, described in Section 4.3. The safety analyses of CheckMate 141 were presented as part of the regulatory submission to the EMA from which a CHMP opinion is expected in ([redacted]) for this indication.

Treatment duration

The median time on therapy for those patients that received at least one dose of study drug was similar for both treatment arms, with patients in the nivolumab and IC arms spending 1.9 months (95% CI, 1.6, 2.3) and 1.9 months (95% CI, 1.6, 2.0), respectively, on therapy.[8] However, after approximately 2 months the proportion of patients still on therapy was higher at each subsequent time-point in the nivolumab arm relative to the IC arm (see Figure 18). Accordingly, a higher proportion of patients were continuing nivolumab as compared to IC of therapy at the time of clinical database lock (18th December 2015), as detailed in Figure 18.

Figure 18: Kaplan-Meier plot of duration of therapy in the all-treated population

Database lock of 18th December 2015.

Abbreviations: CI: confidence intervals; INV Chc: investigator's choice; NIVO: nivolumab
Source: CheckMate 141 CSR (7th June 2016) – Figure 6.1-1[14]

Safety analysis in CheckMate 141

As detailed in Section 4.4, the safety analysis of CheckMate 141 included all randomised patients who received at least one dose of study treatment (all-treated population). AEs were included in the safety analysis if they occurred within 30 days from the day of the last dose received.

Overall safety/tolerability profile

At the time of the clinical database lock (18th December 2015), the majority of patients who received study treatment in CheckMate 141 experienced an AE, regardless of treatment arm.[14] As noted in Section 4.4, a total of 218 deaths in the all randomised population had occurred at this data cut-off point, with 210 deaths having occurred in the all treated population.[14] In the all treated population, disease progression was the most common cause of death and was responsible for 109/132 (82.5%) deaths in the nivolumab arm and 68/78 (87.2%) deaths in the IC arm.[14] A total of two deaths attributable to study drug toxicity were observed in CheckMate 141 (see Table 18); both deaths occurred in the nivolumab arm (Grade 3 pneumonitis and Grade 5 hypercalcaemia).[8] One patient in the IC arm died with a Grade 5 drug-related AE (lung infection), but this death was not attributed to study drug toxicity.[8]

Nivolumab was generally well tolerated by patients in CheckMate 141 compared to IC of therapy, with a lower proportion of patients receiving nivolumab experiencing Grade 3-4 all-causality AEs and SAEs (see Table 18). With regards to drug-related AEs, the proportions of patients experiencing any-grade and Grade 3-4 drug-related AEs, SAEs, and AEs leading to discontinuation were also lower in the nivolumab arm compared to the IC arm (see Table 18).

Table 18: Summary of safety analysis in CheckMate 141[a]

Adverse event, n (%)[b]	Nivolumab (n=236)		IC (n=111)	
Deaths	132 (55.9)		78 (70.3)	
Deaths due to study drug toxicity	2 (0.8)[c]		0[d]	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All causality AEs	229 (97.0)	97 (41.1)	109 (98.2)	58 (52.3)
Drug-related AEs	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
All-causality SAEs	127 (53.8)	66 (28.0)	66 (59.5)	36 (32.4)
Drug-related SAEs	16 (6.8)	11 (4.7)	17 (15.3)	12 (10.8)
All-causality AEs leading to treatment discontinuation	51 (21.6)	27 (11.4)	27 (24.3)	12 (10.8)
Drug-related AEs leading to treatment discontinuation	9 (3.8)	6 (2.5)	11 (9.9)	7 (6.3)

[a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy. [b] AEs were coded using the MedDRA version 18.1. and were graded for severity according to the NCI CTCAE version 4.0. [c] Two deaths in the nivolumab arm (Grade 3 pneumonitis and Grade 5 hypercalcemia) were assessed as related to study drug. [d] In the IC arm, there was 1 death in a patient with a Grade 5 drug-related AE (lung infection) that was not attributed to study drug toxicity.
Database lock of 18th December 2015.

Abbreviations: AEs: adverse events; IC: investigator's choice; MedDRA: Medical Dictionary for Regulatory Activities; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; SAEs: serious adverse events.
Source: CheckMate 141 CSR (7th June 2016) – Table 8.1-1[14]

All-cause and drug-related AEs

AEs of any cause that occurred in at least 10% of patients in either treatment arm are presented in Table 19. The most frequently reported AEs of any cause in the nivolumab arm were fatigue (26.3%), nausea (19.1%), anaemia (18.6%), decreased appetite (18.6%), malignant neoplasm progression (18.2%), and constipation (15.3%) (any grade); and anaemia (5.9%), dyspnoea (5.5%), hyponatremia (4.7%), dysphagia (3.8%), and pneumonia (3.8%) (Grade 3-4).[14] In the IC arm, the most frequently reported AEs of any cause were anaemia (33.3%), fatigue (32.4%), nausea (30.6%), diarrhoea (23.4%), malignant neoplasm progression (22.5%), and asthenia (21.6%) (any grade); and anaemia (8.1%), hyponatremia (8.1%), neutropenia (7.2%), fatigue (6.3%), and pleural effusion (4.5%) (Grade 3-4).[14]

Drug-related AEs that occurred in at least 5% of patients in either treatment arm are presented in Table 20. The most frequently reported drug-related AEs in the nivolumab arm were fatigue (14.0%), nausea (8.5%), rash (7.6%), pruritus (7.2%), decreased appetite (7.2%), diarrhoea (6.8%), and anaemia (5.1%) (any grade); and fatigue (2.1%) (Grade 3-4).[8, 14] In the IC arm, the most frequently reported drug-related AEs were nausea (20.7%), fatigue (17.1%), anaemia (16.2%), asthenia (14.4%), diarrhoea (13.5%), mucosal inflammation (12.6%), and alopecia (12.6%) (any grade); and neutropenia (7.2%) and anaemia (4.5%) (Grade 3-4).[8, 14]

Table 19: All-cause AEs in ≥10% patients in either treatment arm in CheckMate 141[a]

Adverse event, n (%)[b]	Nivolumab (n=236)		IC (n=111)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Total patients with an event	229 (97.0)	97 (41.1)	109 (98.2)	58 (52.3)
General disorders and administration site conditions	134 (56.8)	17 (7.2)	79 (71.2)	16 (14.4)
Fatigue	62 (26.3)	8 (3.4)	36 (32.4)	7 (6.3)
Pyrexia	30 (12.7)	1 (0.4)	16 (14.4)	3 (2.7)
Asthenia	24 (10.2)	5 (2.1)	24 (21.6)	4 (3.6)
Mucosal inflammation	8 (3.4)	0	17 (15.3)	2 (1.8)
Gastrointestinal disorders	129 (54.7)	19 (8.1)	73 (65.8)	11 (9.9)
Nausea	45 (19.1)	1 (0.4)	34 (30.6)	1 (0.9)
Constipation	36 (15.3)	2 (0.8)	20 (18.0)	0
Diarrhoea	35 (14.8)	2 (0.8)	26 (23.4)	3 (2.7)
Dysphagia	29 (12.3)	9 (3.8)	15 (13.5)	3 (2.7)
Vomiting	27 (11.4)	1 (0.4)	14 (12.6)	0
Respiratory, thoracic and mediastinal disorders	107 (45.3)	38 (16.1)	47 (42.3)	12 (10.8)
Cough	32 (13.6)	1 (0.4)	10 (9.0)	0
Dyspnoea	32 (13.6)	13 (5.5)	12 (10.8)	2 (1.8)
Metabolism and nutrition disorders	106 (44.9)	34 (14.4)	56 (50.5)	21 (18.9)
Decreased appetite	44 (18.6)	3 (1.3)	22 (19.8)	4 (3.6)
Hyponatraemia	22 (9.3)	11 (4.7)	14 (12.6)	9 (8.1)
Investigations	81 (34.3)	18 (7.6)	33 (29.7)	9 (8.1)
Weight decreased	31 (13.1)	0	16 (14.4)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	64 (27.1)	8 (3.4)	33 (29.7)	2 (1.8)
Malignant neoplasm progression	43 (18.2)	5 (2.1)	25 (22.5)	2 (1.8)
Skin and subcutaneous tissue disorders	62 (26.3)	1 (0.4)	40 (36.0)	8 (7.2)
Dry skin	11 (4.7)	0	12 (10.8)	0
Alopecia	2 (0.8)	0	14 (12.6)	3 (2.7)
Blood and lymphatic system disorders	58 (24.6)	22 (9.3)	44 (39.6)	20 (18.0)
Anaemia	44 (18.6)	14 (5.9)	37 (33.3)	9 (8.1)

[a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy.
[b] AEs were coded using the MedDRA version 18.1. and were graded for severity according to the NCI CTCAE version 4.0
Database lock of 18th December 2015.

Abbreviations: AE: adverse event; IC: investigator's choice; MedDRA: Medical Dictionary for Regulatory Activities; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.
Source: CheckMate 141 CSR (7th June 2016) – Table 8.5-1[14]

Table 20: Drug-related AEs in ≥5% patients in either treatment arm in CheckMate 141[a]

Adverse event, n (%)[b]	Nivolumab (n=236)		IC (n=111)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Total patients with an event[c]	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
General disorders and administration site conditions	57 (24.2)	6 (2.5)	50 (45.0)	9 (8.1)
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Gastrointestinal disorders	47 (19.9)	3 (1.3)	46 (41.4)	6 (5.4)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Diarrhoea	16 (6.8)	0	15 (13.5)	2 (1.8)
Vomiting	8 (3.4)	0	8 (7.2)	0
Stomatitis	5 (2.1)	1 (0.4)	10 (9.0)	3 (2.7)
Skin and subcutaneous tissue disorders	43 (18.2)	0	32 (28.8)	8 (7.2)
Rash	18 (7.6)	0	5 (4.5)	1 (0.9)
Pruritus	17 (7.2)	0	0	0
Dry skin	7 (3.0)	0	10 (9.0)	0
Alopecia	0	0	14 (12.6)	3 (2.7)
Metabolism and nutrition disorders	32 (13.6)	7 (3.0)	19 (17.1)	5 (4.5)
Decreased appetite	17 (7.2)	0	8 (7.2)	0
Investigations	30 (12.7)	8 (3.4)	13 (11.7)	4 (3.6)
Weight decreased	4 (1.7)	0	6 (5.4)	0
Blood and lymphatic system disorders	17 (7.2)	6 (2.5)	25 (22.5)	14 (12.6)
Anaemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Neutropenia	0	0	9 (8.1)	8 (7.2)
Nervous system disorders	7 (3.0)	1 (0.4)	16 (14.4)	0
Neuropathy	1 (0.4)	0	7 (6.3)	0

[a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy.
[b] AEs were coded using the MedDRA version 18.1. and were graded for severity according to the NCI CTCAE version 4.0
[c] One Grade 5 event (hypercalcemia) in the nivolumab arm and one Grade 5 event (lung infection) in the IC arm were reported. A second death occurred in the nivolumab arm subsequent to Grade 3 pneumonitis.
Database lock of 18th December 2015.

Abbreviations: AE: adverse event; IC: investigator's choice; MedDRA: Medical Dictionary for Regulatory Activities; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.
Source: CheckMate 141 CSR (7th June 2016) – Table 8.5-2[14]

Exposure-adjusted rates of AEs

As noted previously, the study protocol did not permit dose reductions in the nivolumab arm whereas dose reductions were permitted in the IC arm. Consistent with this, a higher proportion of patients who received nivolumab received more than 90% of planned dose intensity compared to patients who received either docetaxel or methotrexate.[14]

When incidence rates of AEs were adjusted for exposure to study drug, the exposure-adjusted rate of AEs occurring in at least 5% of subjects in either treatment group was lower in the nivolumab group than in the investigator's choice group (1607.0 versus 3019.1 incidence rate per 100 person years).[14]

'Select' AEs

'Select' AEs, defined as AEs with a potential immunological cause that are of special clinical interest with the use of nivolumab, were analysed according to organ category (skin, gastrointestinal, endocrine, pulmonary, hepatic, and renal). Most 'select' AEs were Grade 1-2 in severity and were considered drug-related by the investigator.[14] The majority of 'select' AEs were generally manageable using the recommended treatment guidelines for early work-up and intervention.[14]

The most frequently reported any-grade drug-related 'select' AE categories in the nivolumab arm were skin (15.7%), endocrine (7.6%) and gastrointestinal (6.8%).[8] A summary of drug-related 'select' AEs reported in CheckMate 141 is presented in Table 21.

Table 21: Drug-related 'select' AEs in CheckMate 141[a]

'Select' adverse event, n (%)	Nivolumab (n=236)		IC (n=111)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Total patients with an event, by category				
Skin	37 (15.7)	0	14 (12.6)	2 (1.8)
Endocrine	18 (7.6)	1 (0.4)	1 (0.9)	0
Gastrointestinal	16 (6.8)	0	16 (14.4)	2 (1.8)
Hepatic	5 (2.1)	2 (0.8)	4 (3.6)	1 (0.9)
Pulmonary	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/infusion reactions	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal	1 (0.4)	0	2 (1.8)	1 (0.9)
Drug-related 'select' AEs, by category				
Skin				
Rash	18 (7.6)	0	5 (4.5)	1 (0.9)
Pruritus	17 (7.2)	0	0	0
Rash maculo-papular	5 (2.1)	0	1 (0.9)	0
Eczema	2 (0.8)	0	0	0
Skin exfoliation	2 (0.8)	0	0	0
Erythema	1 (0.4)	0	4 (3.6)	1 (0.9)
Exfoliative rash	1 (0.4)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	1 (0.4)	0	2 (1.8)	1 (0.9)
Rash macular	1 (0.4)	0	1 (0.9)	0
Urticaria	1 (0.4)	0	0	0
Dermatitis	0	0	2 (1.8)	0
Endocrine				
Thyroid disorder				
Hypothyroidism	9 (3.8)	0	1 (0.9)	0
Blood thyroid stimulating hormone increase	3 (1.3)	0	0	0
Hyperthyroidism	2 (0.8)	0	0	0
Thyroid function test abnormal	2 (0.8)	0	0	0
Thyroiditis	2 (0.8)	0	0	0
Pituitary disorder				
Hypophysitis	1 (0.4)	1 (0.4)	0	0
Hypopituitarism	1 (0.4)	0	0	0
Adrenal disorder				
Secondary adrenocortical insufficiency	1 (0.4)	1 (0.4)	0	0
Gastrointestinal				
Diarrhoea	16 (6.8)	0	15 (13.5)	2 (1.8)
Colitis	0	0	1 (0.9)	0

'Select' adverse event, n (%)	Nivolumab (n=236)		IC (n=111)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Hepatic				
Alanine aminotransferase increased	2 (0.8)	1 (0.4)	3 (2.7)	1 (0.9)
Aspartate aminotransferase increased	2 (0.8)	0	2 (1.8)	0
Blood alkaline phosphatase increased	2 (0.8)	0	0	0
Transaminases increased	2 (0.8)	1 (0.4)	0	0
Blood bilirubin increased	1 (0.4)	0	0	0
Liver function test abnormal	1 (0.4)	1 (0.4)	0	0
Gamma-glutamyltransferase increased	0	0	1 (0.9)	1 (0.9)
Hepatic enzyme increased	0	0	1 (0.9)	0
Pulmonary				
Pneumonitis	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/infusion reactions				
Infusion-related reaction	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal				
Acute kidney injury	1 (0.4)	0	2 (1.8)	1 (0.9)

[a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy
'Select' AEs were identified based on the following guiding principles: 1) AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies; 2) AEs that may require immunosuppression (e.g. corticosteroids) as part of their management; 3) AEs whose early recognition and management may mitigate severe toxicity; and 4) AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterisation.
Database lock of 18th December 2015.

Abbreviations: AEs: adverse events; IC: investigator's choice.
Source: Gillison *et al.* (2016)[8] and CheckMate 141 CSR (7th June 2016) – Table S.6.14[14]

Conclusions on the safety of nivolumab in patients with platinum-refractory R/M SCCHN

As detailed in Table 18, nivolumab was generally well tolerated in CheckMate 141 with a favourable safety/tolerability profile compared to IC of therapy in terms of the proportion of patients experiencing Grade 3-4 AEs or SAEs (all causality and drug-related). Furthermore, the proportion of patients experiencing drug-related AEs leading to treatment discontinuation were lower in the nivolumab arm compared to the IC arm (see Table 18).

'Select' AEs that represent AEs of particular interest for patients treated with nivolumab did occur in CheckMate 141 (see Table 21). These were mainly Grade 1-2 in severity, and the majority of events were resolved and generally manageable using recommended treatment guidelines. No new safety concerns with nivolumab were identified in CheckMate 141, with a similar safety/tolerability profile observed to that seen with nivolumab (as a monotherapy) in trials for other cancer types.[14]

4.13 Interpretation of clinical effectiveness and safety evidence

As described in Section 3, there is a considerable unmet medical need in England and Wales for patients with R/M SCCHN who have progressed after platinum-based therapy. Currently-available therapies do not offer demonstrable survival benefits in this setting, and life-expectancy for these patients is very low: the 1-year survival rate observed in the comparator arm of CheckMate 141 was 16.6% and median OS was 5.06 months.[8] Based on the results of CheckMate 141, nivolumab could represent an effective and well-tolerated therapy that could significantly improve OS compared to currently-available treatments for patients with R/M SCCHN who have progressed after platinum-based therapy. This would help to address the considerable unmet medical need in this patient population.

4.13.1 Principal findings from the clinical evidence base

The clinical benefits and tolerability of nivolumab in patients with R/M SCCHN who have progressed after platinum-based therapy have been demonstrated in the pivotal phase III RCT, CheckMate 141. The principal findings from this trial supporting the use of in this patient population are summarised below:

- *Overall survival was significantly improved with nivolumab versus IC of therapy (docetaxel, methotrexate or cetuximab)*

In CheckMate 141, nivolumab demonstrated significant improvements in OS compared to the IC arm (HR, 0.70 [97.73% CI, 0.51, 0.96]; p-value = 0.0101), equivalent to a 30% reduction in risk of death with nivolumab versus IC of therapy (see Section 4.7.1).[8] At the interim analysis, treatment with nivolumab was associated with an improvement in median OS of 2.43 months compared to IC of therapy, which represents a considerable extension in life relative to the median OS of 5.06 months achieved in the IC arm (median OS was 1.47-fold greater in the nivolumab arm versus IC of therapy).[8] These meaningful improvements in OS are supported by the more than two-fold improvement in the 1-year survival rate observed in the nivolumab arm (36.0%) compared to the IC arm (16.6%).[8] Furthermore, in CheckMate 141, reductions in the hazard rate of death with nivolumab versus IC of therapy were observed, regardless of HPV-p16 status or PD-L1 expression (see Section 4.8).

Long-term survival benefits with nivolumab have been observed in the other cancer indications that have been investigated (advanced NSCLC, aRCC and advanced melanoma), and for which data from longer follow-up are available.[10-12] Of these other indications, feedback from UK clinicians suggests that patients with squamous advanced NSCLC are most representative of R/M SCCHN, due to the similar tumour histology, patient characteristics (e.g. age, smoking status – see Appendix 5 for a comparison of the eligibility criteria and baseline characteristics between CheckMate 141 and advanced squamous NSCLC nivolumab trials) and patient prognosis (squamous NSCLC patients in the comparator arm of CheckMate 017 trial, docetaxel 75 mg/m^2 Q3W, had a median OS of 6.0 months).[7, 105] In the absence of longer term data in the SCCHN indication, specifically[i], estimates of longer-term survival from advanced squamous NSCLC are therefore considered to be a reasonable proxy for long-term survival with nivolumab as a treatment for R/M SCCHN. The data from advanced squamous NSCLC are summarised below:

[i] The CheckMate 141 trial was initiated based on preclinical data and results from CheckMate 003: a phase I dose escalation study that included patients with select previously-treated, advanced solid tumours, including NSCLC, amongst others, but not SCCHN.

- 3-year survival rate from **CheckMate 003**; phase I; advanced, squamous NSCLC (n=18, 3 mg/kg nivolumab): 28%[106]

- 18-month survival rate from **CheckMate 063**; phase II; platinum-refractory, advanced, squamous NSCLC (n=117, 3 mg/kg nivolumab): 27%[10]

- 18-month survival rate from **CheckMate 017**; phase III; platinum-refractory, advanced, squamous NSCLC (n=135, 3 mg/kg nivolumab): 28%[10]

The plateauing of the nivolumab Kaplan-Meier curve in CheckMate 141 at a higher level, as compared to IC of therapy (see Figure 10), is suggestive that patients with R/M SCCHN may also experience long-term survival benefits following treatment with nivolumab as has been demonstrated in these other indications. Longer follow-up of patients in the CheckMate 141 study would look to confirm this (see Section 4.14).

- *Treatment with nivolumab was associated with a higher ORR compared to IC of therapy, and may allow patients to maintain levels of HRQoL and symptom control to a greater degree than IC of therapy*

The ORR was more than doubled for nivolumab versus IC of therapy (13.3% [95% CI, 9.3, 18.3] compared to 5.8% [95% CI, 2.4, 11.6]) with a higher proportion of patients in the nivolumab arm achieving a best overall response of either a complete or partial response, as compared to the IC arm (see Section 4.7.2).[9]

Furthermore, evidence from CheckMate-141 suggests that whereas IC of therapy is associated with declines in functioning and worsening of symptoms, nivolumab may stabilise patient HRQoL. Patients treated with nivolumab exhibited no meaningful changes (i.e. ≥10 points) indicative of worsening symptoms across the majority of EORTC QLQ-C30 and QLQ-H&N35 scales in the first 21 weeks of follow-up (see Section 4.7.2). In contrast, patients receiving IC of therapy experienced meaningful worsening across numerous scales in both the EORTC QLQ-C30 and QLQ-H&N35.[14] Significant differences between treatment arms at both Weeks 9 and 15 in favour of nivolumab versus IC of therapy were observed for physical functioning, role functioning, social functioning, fatigue, dyspnoea and appetite loss (EORTC QLQ-C30), and pain and sensory problems (EORTC QLQ-H&N35) ($p<0.05$, see Section 4.7.2).[22]

Together, the results from these secondary (ORR) and exploratory (HRQoL) outcomes provide further supportive evidence of nivolumab as an effective therapy.

- *Nivolumab was well tolerated by patients in CheckMate 141 and demonstrated a more favourable safety/tolerability profile compared to IC of therapy*

In CheckMate 141, the proportion of patients experiencing a drug-related, Grade 3-4 AE or SAE in the nivolumab arm was less than half that reported in the IC arm (drug-related, Grade 3-4 AEs: 13.1% nivolumab versus 35.1% IC of therapy; drug-related, Grade 3-4 SAEs: 4.7% nivolumab versus 10.8% IC of therapy; see Section 4.12).[8, 14] In addition, nivolumab was associated with a lower proportion of patients experiencing drug-related AEs of any grade leading to treatment discontinuation compared to IC of therapy (3.8% nivolumab versus 9.9% IC of therapy).[14] No new safety concerns with nivolumab were identified in CheckMate 141, with a similar safety/tolerability profile observed to that seen with nivolumab (as a monotherapy) in trials for other cancer types, and the majority of 'select' AEs that did occur were resolved and generally manageable.

4.13.2 End-of-life criteria

The clinical evidence presented from CheckMate 141 supports the consideration of nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy as a 'life-extending medicine at the end of life,' in accordance with the revised NICE end-of-life criteria.[17]

The life-expectancy of patients with R/M SCCHN who have progressed after platinum-based therapy is estimated to be 5.1 months based on the median OS observed in the IC arm of the CheckMate 141 trial.[8] This is consistent with expert clinician feedback which estimated life-expectancy to be less than 6 months for patients treated with currently-available therapies in clinical practice and is considerably lower than the 24 months cited in the NICE end-of-life criteria.[6, 7, 17] Furthermore, mean OS predicted in the economic model for each of the comparators included in this appraisal was well below this 24-month threshold (see Table 27 in Section 5.3.2), regardless of the parametric survival distribution that was used.

At the interim analysis of CheckMate 141, median OS was extended by 2.43 months in the nivolumab arm (7.5 months [95% CI, 5.5, 9.1]) versus the IC arm (5.1 months [95% CI, 4.0, 6.0]).[8] This extension in life is just below the 3 months that are *normally* required of therapies to meet the NICE end-of-life criteria, however, the following points should be considered:

1. For patients with platinum-refractory R/M SCCHN, this extension to life represents a considerable survival benefit (1.47-fold greater median OS with nivolumab) compared to that achieved with IC of therapy alone

2. The improvement in OS observed with nivolumab was considered to be statistically significant, with nivolumab associated with a significant 30% reduction in the risk of death compared to IC of therapy (HR, 0.70 [97.73% CI, 0.51, 0.96]; p-value = 0.0101)[8]

3. Importantly, if the long-term survival benefits of nivolumab seen in other cancer indications are replicated in R/M SCCHN, the survival benefit for nivolumab versus IC, in terms of mean OS, is likely to increase. The median value for OS does not necessarily represent the durable survival benefit that could potentially be achieved by some patients[18]

4. The mean OS benefit with nivolumab was estimated to be greater than 3 months compared to the IC arm using extrapolated data from CheckMate 141 in the economic model (see Table 27 in Section 5.3.2), regardless of the parametric survival distribution used

Based on mean OS predicted by the economic model, nivolumab is expected to provide an extension in life that is greater than the 3 months cited in the NICE end-of-life criteria (see Table 22). Notably, both end-of-life criteria were met using any of the parametric survival distributions that were explored for the economic analysis (see Table 27 in Section 5.3.2).

Table 22: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life-expectancy, *normally* less than 24 months	Mean OS predicted in the base case of the cost-effectiveness analysis was 8.4 months for IC (see Table 27 in Section 5.3.2). A mean OS of less than 24 months for the IC arm was predicted for all parametric survival distributions that were explored (see Table 27 in Section 5.3.2).
There is sufficient evidence to indicate that the treatment offers an extension to life, *normally* of at least an additional 3 months, compared with current NHS treatment	Mean OS predicted in the base case of the cost-effectiveness analysis was 17.7 months for nivolumab (see Table 27 in Section 5.3.2), representing an extension in mean OS of 9.3 months relative to IC of therapy. An extension in OS of more than 3 months was predicted for each parametric survival distribution that was explored (see Table 27 in Section 5.3.2).

Abbreviations: IC: investigator's choice; OS: overall survival.
Source: Gillison *et al.* (2016)[8] and CheckMate 141 CSR (7th June 2016)[14]

4.13.3 Strengths and limitations of the clinical evidence

Strengths, limitations and consistency with the decision problem

Clinical evidence supporting the use of nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy is presented in this submission from the phase III RCT CheckMate 141 (n=361; see Section 4). Patients considered eligible for treatment with nivolumab under the anticipated indication for SCCHN are expected to have progressed after having received platinum-based therapy. The clinical evidence presented in this submission is therefore consistent with the patient population expected to receive nivolumab in clinical practice, and is also consistent with the evidence submitted in support of the regulatory application for nivolumab as a treatment for R/M SCCHN.

CheckMate 141 is an international, multicentre phase III RCT that provides direct head-to-head evidence for the efficacy and safety of nivolumab versus IC of therapy, which included docetaxel and methotrexate – both of which are relevant comparators in this appraisal.[1, 8] The use of IC as a comparator has previously been accepted by health authorities in cases when a placebo or best supportive care control arm is considered unethical or unfeasible and there is no well-recognised standard-of-care therapy.[107]

Expert clinical opinion is that the three therapies used in the IC arm can be considered equivalent in terms of OS, and a phase II trial of docetaxel and methotrexate in recurrent SCCHN also indicates equivalent survival between these therapies.[6, 58] The IC arm of CheckMate 141 did not however include paclitaxel – another taxane that is included as a comparator in this appraisal (see Section 1.1). Limited RCT evidence is available for the use of paclitaxel in patients with platinum-refractory R/M SCCHN; however, feedback from clinicians suggests that paclitaxel may also be considered equivalent to the other therapies included in the final scope.[7]

Given the lack of additional clinical trial data identified in the SLR that could adequately inform direct or indirect comparisons between nivolumab and the comparators included in this appraisal (see Section 4.10), CheckMate 141 can be considered to provide estimates, most relevant to UK practice, of the treatment effect for nivolumab versus each of the comparators included in this appraisal.

The relevance of results from the IC arm of CheckMate 141 to the decision problem addressed in this appraisal (with regards to comparators) is summarised below:

- The IC arm of CheckMate 141 included docetaxel and methotrexate; the majority of patients treated in the IC arm received either docetaxel (47%) or methotrexate (41%), with few patients receiving cetuximab (12%)[8, 9]
- The comparators included in the IC arm of CheckMate 141 are considered to be equivalent in terms of OS; paclitaxel is also considered to have equivalent efficacy[6, 7]
- Equivalent survival efficacy between methotrexate and docetaxel has been demonstrated in a phase II trial of patients with R/M SCCHN (albeit not platinum-refractory, specifically)[58]
- Limited additional RCT data is available that could be used to indirectly compare therapies included in the appraisal scope as treatments for platinum-refractory R/M SCCHN (see Section 4.10)

As detailed in Section 4.6, CheckMate 141 is of high quality, using appropriate methods of randomisation and data analysis. Although the trial was open-label in design, the risk of detection bias was mitigated by the use of an objective measure of efficacy (OS; time to death) as the primary endpoint. OS is the most relevant and meaningful outcome for patients with R/M disease and is considered the gold standard endpoint for trials of anti-cancer therapies.[65] CheckMate 141 was primarily designed to detect statistically significant differences in OS between the nivolumab arm and the IC arm, and as such provides robust estimates of OS for each treatment arm (see Section 4.4).

Secondary outcomes examined in CheckMate 141 included PFS and ORR, as determined using RECIST version 1.1; assessments of HRQoL using appropriate, validated measures were also included as exploratory outcomes (see Section 4.3.3). The use of RECIST in cancer trials is recommended by the EMA and provides an objective measure of tumour response and PFS – the latter point being particularly pertinent given the open-label design of CheckMate 141.[65] However, it should also be noted that in clinical practice, response to therapy will most likely be assessed based on clinical judgement rather than radiological assessments and that RECIST may have limitations as a method of evaluating clinical benefit in terms of response or progression with immune-checkpoint inhibitors (see Section 4.3.3).

Taken together in terms of intervention, comparators, patient population and outcomes assessed, the evidence presented in this submission from the CheckMate 141 trial is relevant for the decision problem of this appraisal, as detailed in Section 1.1.

Generalisability of results to the UK

The IC comparator arm included in CheckMate 141 consisted of docetaxel, methotrexate or cetuximab.[8, 9] In UK clinical practice, docetaxel is most routinely used for the treatment of patients with platinum-refractory R/M SCCHN, with paclitaxel (another taxane, but without European marketing authorisation for use in SCCHN)[108] and methotrexate also used to a lesser extent.[5, 7] Cetuximab monotherapy is not believed to be used in UK clinical practice in the platinum-refractory setting and is not included as a relevant comparator in this appraisal (see Section 3); however, only a small proportion (12%) of patients treated in the IC arm of CheckMate 141 received cetuximab.[6, 14]

The survival benefit observed with nivolumab versus IC of therapy in CheckMate 141 is therefore considered to be generalisable to current practice in the UK, with a similar median OS observed

in the IC arm to that expected in clinical practice with currently-available therapies (less than 6 months), based on expert clinician feedback.[6] Exploratory analyses of OS by intended therapy for the IC arm are also presented in Section 4.8, with nivolumab demonstrating improvements in OS versus both docetaxel (n=54) and methotrexate (n=52), respectively.

The patient population included in CheckMate 141 is representative of the UK patient population, as outlined in Section 4.5.3. Almost half of patients randomised in CheckMate 141 were enrolled at European study sites (47.4%), with 34 patients (9.4%) in the all-randomised population treated at UK study sites. Patients in the all-randomised population were typically 60-years of age, male (83.1%), white (83.1%) and former/current smokers (76.5%) (see Table 13) and thus match the demographic characteristics of patients expected to present in UK clinical practice, as described in Section 3.1.

Eligibility for inclusion in CheckMate 141 was restricted to patients with an ECOG performance status of 0 or 1 (see Section 4.3.2). In clinical practice, most patients who receive single-agent chemotherapy for R/M disease are expected to have an ECOG performance status of 0 or 1, as evidenced by a medical chart review of metastatic SCCHN patients in the UK (n=220), in which over 80% of patients who received systemic therapy had a performance status of 0 or 1.[5]

Finally, in subgroup analyses of CheckMate 141, nivolumab demonstrated a reduced hazard rate of death versus IC of therapy regardless of HPV-p16 status or tumour PD-L1 expression (≥1% or <1%), with improvements also observed across selected baseline characteristics, including age (<65 or ≥65 to <75 or ≥75) and ECOG performance status (0 or ≥1) (see Section 4.8).[8] These subgroup analyses indicate that nivolumab should therefore be considered an effective treatment for all patients covered by the anticipated indication.

4.14 Ongoing studies

The next database lock of the CheckMate 141 trial is expected in [redacted] from which updated efficacy analyses will be conducted.

In addition to CheckMate 141, nivolumab RCTs that include patients with R/M SCCHN are soon to commence (CheckMate 651, CheckMate 714 and RTOG 3504); however, these trials investigate the use of nivolumab in combination with either ipilimumab (CheckMate 651 and CheckMate 714) or chemotherapy (RTOG 3504), and with the exception of CheckMate 714, do not include patients with platinum-refractory SCCHN.[109-111] Results of these trials are not expected within the next 12 months.[109-111]

5 Cost effectiveness

***De novo* cost-effectiveness model**

- The cost-utility of nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy was evaluated using a partitioned survival approach. The model included three health states: *progression free, progressed disease*, and *death*; and is consistent with other models submitted to NICE in R/M SCCHN and other nivolumab indications
- Nivolumab was compared to docetaxel, paclitaxel and methotrexate; clinical data from the IC arm of the CheckMate 141 trial were applied to each comparator in order to preserve study randomisation and statistical power
- OS and PFS estimates were extrapolated from CheckMate 141 trial data using appropriate survival analyses; TTD from this trial was also used to determine the duration of treatment for nivolumab and comparators in the model
    - Alternative clinical stopping rules whereby treatment was stopped after 1, 2 or 3 years for patients who had not yet progressed were explored in scenario analyses – stopping treatment for patients who do respond may be feasible in practice due to the unique mechanism of action of immune-checkpoint inhibitors in restoring anti-tumour immunity, as demonstrated by the durable benefits observed in other cancer indications after stopping treatment with nivolumab
- Treatment-dependent, health-state utilities for the *progression-free* and *progressed disease* states were derived from EQ-5D-3L data collected from patients in the CheckMate 141 trial; disutilities for AEs were also included
- Resource use and costs included in the model were based on information from CheckMate 141, previous technology appraisals and published sources identified in a SLR
- Feedback from UK clinicians was sought in order to validate assumptions and inputs included in the model

Base case cost-effectiveness results

- Nivolumab was found to be associated with higher costs but also higher life-years gained and higher QALYs than docetaxel, methotrexate or paclitaxel.
- Under the base case assumptions nivolumab was seen to be associated with ICERs of between £34,777 and £34,908 when nivolumab was provided with the confidential PAS; these ICERs are well below the cost-effectiveness threshold of £50,000 per QALY considered for therapies meeting end-of-life criteria.

Sensitivity analyses

- ICER estimates obtained from probabilistic sensitivity analysis to take account of combined uncertainty in the model were similar to the base case deterministic ICERs
- Of parameters explored in deterministic sensitivity analysis, the utility value for *progressed disease* with nivolumab was found to be the most influential parameter on the ICERs
- Scenario analyses were conducted to explore the impact of clinical stopping rules, different time horizons and alternative parametric distributions for OS, PFS and TTD, amongst other sensitivity analyses. In the vast majority of scenario analyses the ICERs for nivolumab (with PAS) versus all comparators were found to be well below a cost-effectiveness threshold of £50,000 per QALY

Conclusion

- Nivolumab was found to represent a cost-effective use of NHS resources when considered with a PAS and as an end-of-life medicine, being associated with ICERs well below the £50,000 per QALY threshold versus all comparators

5.1 Published cost-effectiveness studies

Identification of studies

An SLR was conducted in order to identify evidence to support the development of a cost-effectiveness model for nivolumab as a treatment for platinum-refractory R/M SCCHN. A single review was performed to identify relevant studies in SCCHN, including: published economic evaluations, studies reporting cost/resource use data, and studies reporting utility values.

Literature was searched in electronic databases recommended by NICE.[71] The following electronic databases were searched on the 14th September 2015:[i]

- Embase®
- MEDLINE®
- MEDLINE® In-Process
- EconLit
- The Cochrane Library:
    - National Health Service Economic Evaluations Database (NHS EED)
    - Cochrane Health Technology Assessment Database (HTAD)

Evidence published from 2005–2015 were included in the review. Congress abstracts (from congresses held over the prior three years: 2013–2015) were also hand searched to identify recent economic evidence which may not have been published as full-text journal articles at the time of the database search.

The relevant congresses screened included:

- American Society of Clinical Oncology (ASCO)
- ASCO Quality Care Symposium (ASCO-QoC)
- Academy of Managed Care Pharmacy (AMCP)
- European Society for Medical Oncology (ESMO)
- American Head and Neck Society (AHNS)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR – Europe and International)

The full search strategy for the SLR is presented in Appendix 6. Articles identified from the search were first screened based on the title and abstract (Stage 1) against predefined eligibility criteria (see Table 23). Full-texts of all articles that met the eligibility criteria were then obtained and were subsequently screened for inclusion using the same eligibility criteria (Stage 2). Screening was undertaken by a single reviewer and then checked by a second, independent reviewer.

[i] Embase® and MEDLINE® were searched via the Embase.com platform; MEDLINE® In-Process was searched via the PubMed.com interface; EconLit was searched via the AEAweb.org platform

Table 23: Eligibility criteria for the economic systematic literature review

Eligibility domain	Inclusion criteria	Exclusion criteria
Population	Adult patients with stage III/IV SCCHN	-
Intervention(s)	• Nivolumab • Docetaxel • Methotrexate • Paclitaxel And other approved/ investigational agents: cetuximab; fluorouracil; bleomycin; cisplatin; cetuximab; temoporfin; cabazitaxel; irinotecan; afatinib; zalutumumab; gefitinib; carboplatin; lapatinib; bevacizumab; panitumumab; nimotuzumab; capecitabine; erlotinib; canertinib; mpdl3280a; sorafenib; axitinib; buparlisib; mk-1775; pembrolizumab; medi4736; oxaliplatin; epirubicin; gemcitabine; vinorelbine; ifosfamide; pemetrexed; advexin; regorafenib	-
Comparator(s)[a]	• Any active pharmacological agent • Therapy of investigator's choice • Placebo • Best supportive care	-
Outcomes(s)	• Economic outcomes such as cost-effectiveness and/or cost utility including ICER/ICUR, cost/QALY, cost/LYG, cost/DALY, sensitivity analyses results • Direct/indirect costs, resource use data reported in economic evaluations • QALY, DALY, LYG • Utility/disutility data associated with disease and adverse events including EQ-5D, time trade off, standard gamble, etc.	-
Study design 1 (Published economic evaluations)	• Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimisation analyses • Budget impact models • Cost consequence studies • All economic evaluation studies based on models	• Case studies • Case series • Case reports
Study design 2 (Cost/resource use studies)	• Cost studies/surveys/analyses • Database studies collecting cost data (e.g. claims databases and hospital records) • Resource surveys	
Study design 3 (Utility studies)	• Studies reporting utility data[b]	
Other considerations	• Full-text articles published in English language • Published 2005–2015	• Full-text articles in any other language to English

[a] Only applicable to published economic evaluations
[b] Studies exclusively reporting HRQoL data were not included in this review

Abbreviations: DALY: Disability Adjusted Life Years; EQ-5D: EuroQol-5D; HRQoL: health-related quality of life; ICER: Incremental Cost-Effectiveness Ratio; ICUR: Incremental Cost-Utility ratio; QALY: Quality Adjusted Life Years.

Description of identified studies

A total of 3,469 unique articles were identified in the review once duplicates had been removed, of which 44 articles (representing 43 unique studies) met the eligibility criteria and were included in the review. The results of the review are presented in the PRISMA diagram provided in Figure 19.

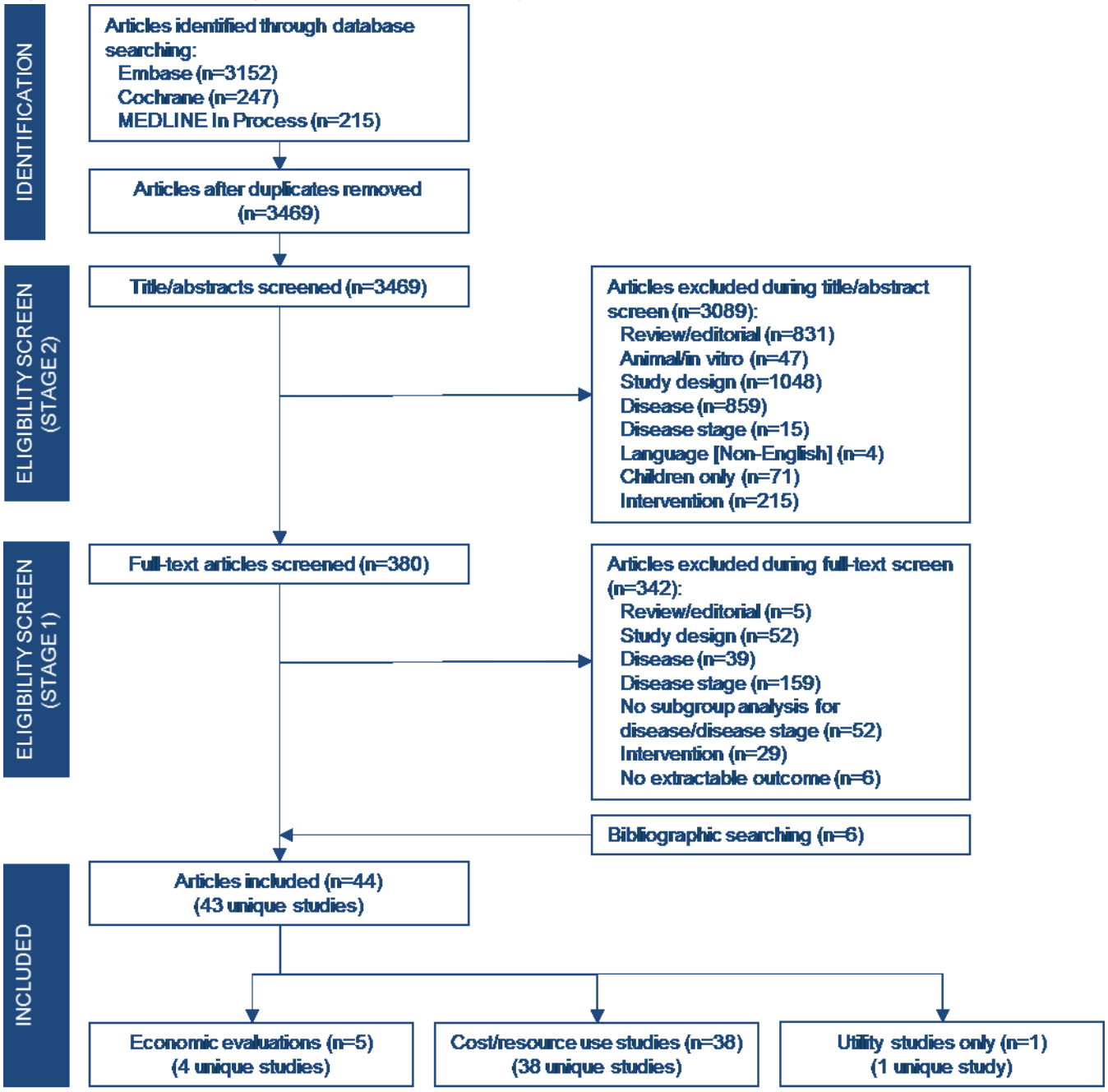
Further details on the included articles are presented in the relevant sections of the submission, with published economic evaluations described below, utility studies in Section 5.4.3 and cost/resource use studies in Section 5.5.1. A list of articles excluded during the screening of full-text articles (Stage 2) is presented in Appendix 7.

Economic evaluations identified in the review

In total, four published economic evaluations were identified in the SLR (see Appendix 8).[112-115] None of these economic evaluations evaluated the cost-effectiveness of nivolumab or included patients with R/M SCCHN who had progressed after platinum-based therapy. In addition, no studies were identified from the UK NHS/PSS perspective.

Critical appraisals of each published economic evaluations included in the SLR were conducted using the checklist adapted from Drummond *et al.* (1996),[116] as recommended by NICE.[71] The results of these critical appraisals are presented in Appendix 9.

Figure 19: PRISMA diagram for the economic systematic literature review



Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

5.2 De novo analysis

No relevant previously published cost-effectiveness studies were identified by the SLR reported in Section 5.1. A *de novo* cost-effectiveness model was therefore constructed, as described in the following sections.

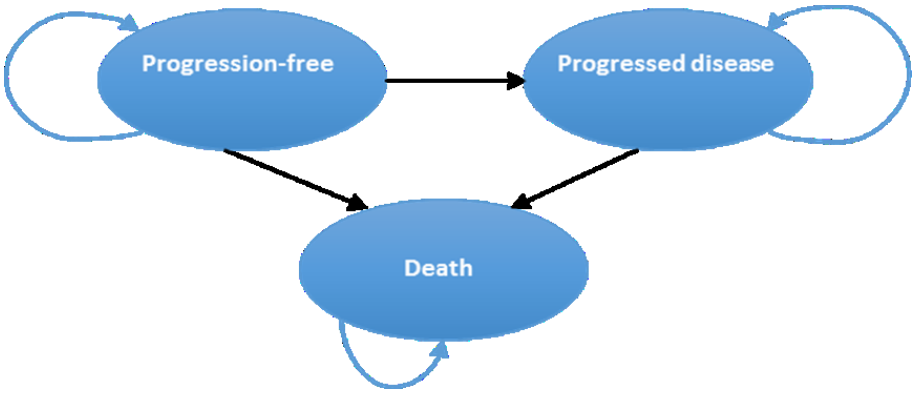
5.2.1 Patient population

The economic evaluation considers adults with R/M SCCHN who have progressed after platinum-based therapy, which is consistent with the study population of CheckMate 141.[8, 9] This population is also consistent with the anticipated indication for nivolumab in SCCHN and the population outlined in the final scope issued by NICE for this appraisal.[1]

5.2.2 Model structure

The *de novo* health economic model was constructed in Microsoft Excel and is a cohort-based partitioned survival model consisting of three mutually exclusive health states: *progression-free* (PF), *progressed disease* (PD) and *death* (see Figure 20). The model structure is in line with the clinical pathway of care for the treatment of R/M SCCHN and is consistent with previous economic evaluations submitted to NICE in R/M SCCHN [TA172, 2009] and other evaluations of nivolumab appraised by NICE [ID811, ID900].[19, 20, 23]

Figure 20: Model structure



Patients with R/M SCCHN who had progressed after platinum-based therapy entered the model in the PF health state and were treated with either nivolumab, docetaxel, methotrexate or paclitaxel. At the end of each cycle, a patient remained in the PF health state or entered either the PD or death states (see Figure 20). Patients could not improve health states, which reflects the progressive nature of the condition and is consistent with previous economic modelling in R/M SCCHN. Disease progression was defined by RECIST version 1.1, as per the CheckMate 141 trial. The death state is an absorbing state.

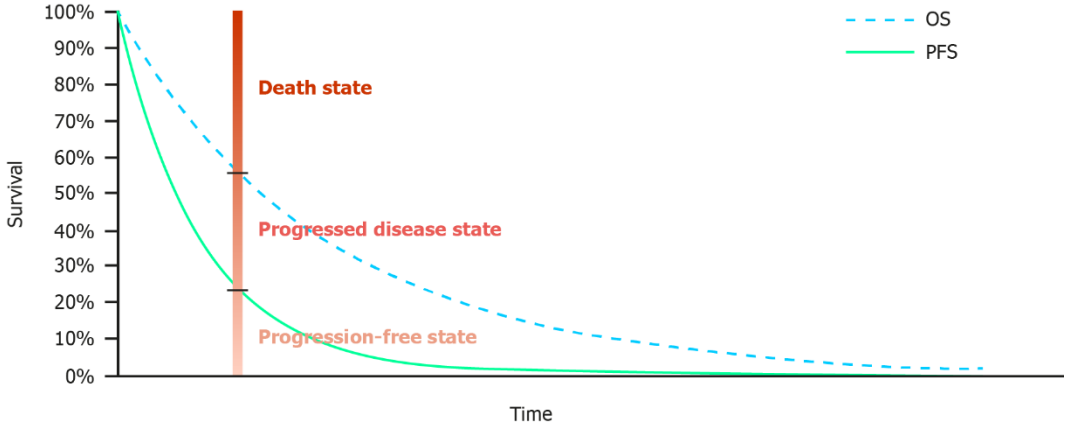
The occupancy of each health state was estimated using the partitioned survival method (as per previous oncology appraisals),[19, 20] whereby the number of patients in each state was derived directly from the cumulative survival probabilities for PFS and OS:

- The proportion of patients occupying the PF state was calculated as the proportion alive and progression-free (based on PFS curve)

- The proportion of patients occupying the PD state was calculated as the proportion alive (based on OS curve) minus the proportion of patients alive and progression-free (based on PFS curve)
- The proportion of patients occupying the death state was calculated as the proportion who had died (based on OS curve)

The use of partitioned survival method to derive the occupancy of each health state is illustrated in the schematic shown in Figure 21. The partitioned survival approach allows for modelling of OS and PFS based on study-observed events, which is expected to accurately reflect disease progression and the long-term expected survival profile of patients treated with nivolumab.

Figure 21: Schematic representation of the partitioned survival method



Abbreviations: OS: overall survival; PFS: progression-free survival.

The duration of treatment in the model was based on the TTD curves for nivolumab (for the nivolumab treated patients) and the IC arm (for docetaxel, paclitaxel and methotrexate treated patients) from the CheckMate 141 trial, as described in Section 5.3.4.

Features of the *de novo* analysis

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. Costs and disutilities associated with AEs are estimated per episode, and are applied once at the beginning of the first-cycle based on the proportion of patients in each treatment arm experiencing each AE (see Section 5.3.6 for a full description of how AEs are applied in the model).

The analysis was conducted from the perspective of the NHS and PSS in England and Wales over a time horizon of 20 years, equivalent to 260× 4-week cycles. This time horizon was chosen in line with the maximum expected survival of the cohort predicted by parametric survival analyses and therefore captures all expected costs and benefits. A half-cycle correction was implemented to mitigate bias that can result from the modelling of continuous time as discrete cycles. The impact of using shorter and longer time horizons (10 years, 15 years and 25 years) were also explored in scenario analyses, with all other settings as per the base case analysis (see Scenario 11a–c in Section 5.8.3)

Features of the *de novo* analysis and their justifications are described in Table 24.

Table 24. Features of the *de novo* analysis

Factor	Chosen values	Justification
Time horizon	20 years	Time horizon is sufficiently long enough for >99% of patients in the model to have died
Cycle length	4 weeks	From Week 9 of the CheckMate 141 trial tumour assessments were performed every 6 weeks. Dosing of nivolumab is every 2 weeks and for comparators dosing ranges from once weekly to once every three weeks. A 4-week cycle length was therefore chosen based on pragmatic consideration of these factors.
Half-cycle correction	Yes	Mitigate bias due to cycle length
Were health effects measured in QALYs; if not, what was used?	Yes	Consistent with the NICE reference case[25]
Discount of 3.5% for utilities and costs	Yes	Consistent with the NICE reference case[25]
Perspective (NHS/PSS)	Yes	Consistent with the NICE reference case[25]

Abbreviations: NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PPS: Personal Social Services; QALYs: quality-adjusted life years.

5.2.3 Intervention technology and comparators

Nivolumab

Nivolumab has been considered within the economic evaluation as per the anticipated licensed indication in SCCHN (see Section 2.2). Nivolumab has therefore been modelled with a posology of 3 mg/kg as a 60-minute infusion, Q2W. The licence also specifies that nivolumab treatment should be continued until clinical benefit is no longer observed and treatment beyond progression with nivolumab was permitted in the CheckMate 141 trial (see Section 4.3.1). This aspect of anticipated use with nivolumab is reflected through the use of the TTD curve to model time on treatment (see Section 5.2.4).

Comparators

In line with the final scope issued by NICE for this appraisal, the comparators against which the cost-effectiveness of nivolumab has been evaluated are docetaxel, paclitaxel and methotrexate.[1] As described in Section 3.2, there is no single, universally-accepted therapy for the treatment of patients with R/M SCCHN who have progressed after platinum-based therapy, with the choice of therapy dependent on the availability of appropriate clinical trials (in order to possibly receive investigational therapies), prior chemotherapy received, patient fitness and tolerability of specific toxicities.[6, 7] In UK clinical practice (i.e. outside of a clinical trial), treatment in the platinum-refractory setting would most likely be with a taxane (docetaxel or paclitaxel), or methotrexate if a taxane was clinically inappropriate due to tolerability issues or prior taxane therapy.[6] Single-agent docetaxel (Q3W) is predominantly used in UK clinical practice however paclitaxel (QW) may also be used for patients who are not fit enough to receive treatment with docetaxel and have not received prior taxane therapy.[7]

In the IC comparator arm of the CheckMate 141 trial the vast majority of patients received docetaxel or methotrexate (47% and 41%, respectively; see Section 4.3).[8, 9] Clinical parameters included in the model (OS, PFS, TTD, incidence of AEs) for docetaxel and methotrexate have been derived from the total IC arm of CheckMate 141 study in order to maintain sample size and preserve trial randomisation. Clinical equivalence between these therapies with regards to efficacy in patients with platinum-refractory R/M SCCHN has been confirmed by expert clinician feedback and is supported by data from a phase II clinical trial.[6, 58] Clinical data from the IC arm of CheckMate 141 have also been used for the comparison of nivolumab to paclitaxel. Docetaxel and paclitaxel are both taxanes and are often grouped together in discussion of clinical agents for the treatment of R/M SCCHN; an assumption of clinical equivalence is therefore considered appropriate and is supported by UK clinical opinion.[4, 7] Furthermore, the clinical SLR identified limited RCT evidence for paclitaxel as a monotherapy for the treatment of platinum refractory R/M SCCHN (see Section 4.1), thereby necessitating an assumption of equivalence to docetaxel in order to model this comparator.

Treatment-related costs (drug acquisition, administration and monitoring) have been applied to each individual comparator and are detailed in Section 5.5.1 alongside dosing administration frequencies for all treatments included in the model.

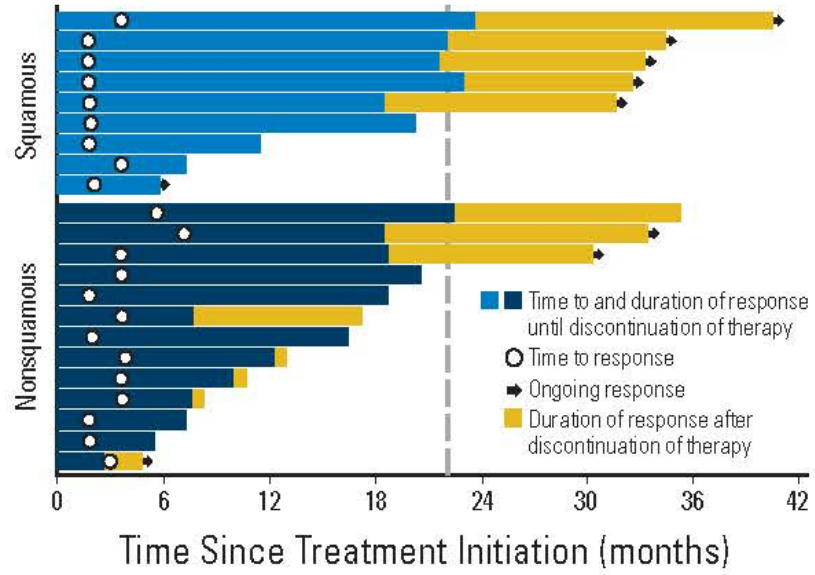
5.2.4 Treatment beyond progression and time to discontinuation

In the model, all patients were assumed to be treated until trial-observed treatment discontinuation rather than until disease progression, with treatment-related costs accrued accordingly. Accordingly, patients in the PD state could still be receiving treatment despite having disease progression. The treatment of patients beyond disease progression is consistent with the trial protocol for CheckMate 141 (see Section 4.3), and the licensed posology for nivolumab which states that "*treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient*."[13, 14] This is in recognition of the possibility that patients treated with immune-checkpoint inhibitors may display signs of initial progression before going on to experience a clinical response (i.e. they experience an "unconventional immune-related response") as described in Section 2.1.This approach to modelling time on treatment was selected in order to provide a realistic estimation of treatment-related costs based on actual treatment duration.

In addition to this base case, clinical stopping rules were explored in scenario analyses (see Scenarios 1–3 in Section 5.8.3), to reflect the possibility that, due to the unique mechanism of action of immune-checkpoint inhibitors in restoring anti-tumour immunity, it may be feasible to stop treatment with nivolumab for patients who have not yet progressed and still maintain clinical benefit. Evidence to support the stopping of treatment for patients who are responding to nivolumab is available from the CheckMate 003 trial in which treatment was continued up to 96 weeks.[106] Ongoing responses after treatment cessation were observed in this trial for patients with advanced NSCLC who had completed 96 weeks of therapy with nivolumab (see Figure 22).

Additionally, a scenario analysis was conducted to explore the impact of assuming no treatment beyond progression with nivolumab or the comparator therapies in which time on treatment was modelled using PFS curves rather than TTD (see Scenario 10 in Section 5.8.3)

Figure 22: Swimmers plot from CheckMate 003



Squamous NSCLC (n=9) and non-squamous NSCLC (n=13) treated with nivolumab
Vertical dashed line at 22 months indicates maximum planned duration of continuous nivolumab therapy. Eighteen responders discontinued nivolumab therapy for reasons other than disease progression, including: completion of maximum cycles (n=7), adverse events (n=8), withdrawal of consent (n=2), and other (n=1)

Abbreviations: NSCLC: non-small cell lung cancer.
Source: Gettinger *et al.* (2015)[106]

5.3 Clinical parameters and variables

5.3.1 Overall method for modelling survival

The primary source of clinical data for the economic model was patient-level data from the CheckMate 141 trial. As noted in Section 5.2.3, trial data from the IC arm was applied to each comparator included in the model, as these are considered to represent the most robust estimates of OS, PFS and TTD for the comparator therapies.

As the follow-up period in CheckMate 141 was shorter than the required length of the economic analysis (i.e. not all patients had died, progressed or discontinued treatment in the trial), extrapolation of the OS, PFS and TTD data from CheckMate 141 was needed in order to estimate the proportion of patients in each health state across the time horizon of the model. The identification of parametric survival models for OS, PFS and TTD was therefore undertaken. Guidance from the NICE Decision Support Unit (DSU) were considered to identify the most appropriate parametric survival modelling approach for OS, PFS and TTD.[24] The guidance is summarised below:

1. Generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach – the assumption should be tested in order to indicate whether it may be preferable to separately fit parametric models to each treatment arm or to allow for time-varying hazard ratios.

2. Testing the proportional effects assumption: the log-cumulative hazards, log-cumulative odds and standardised normal curve plots should be assessed to determine if the trial

survival data indicate proportional effects. This should be done by visual inspection to determine if the survival curves are parallel to one another.

In the event that proportional effects holds, a comprehensive range of parametric survival distributions should be explored. These include the standard exponential, Weibull, Gompertz, lognormal, loglogistic and generalised gamma models, as well as a series of flexible models such as spline-based models.

In the event proportional effects does not hold, both independent survival models and single survival models adjusted for shape and scale should be assessed.

3. Within the various parametric survival distributions explored (whether single or independent models), the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit statistics and visual inspection against Kaplan Meier curves should be assessed to identify the best-fitting survival models

4. Finally, the choice of parametric model should be validated for clinical plausibility of both short-term and long-term extrapolations

Given that individual patient level data were available from the CheckMate 141 trial for both nivolumab and the IC arm, there was not a requirement to assume proportional hazards, though this was tested for as per the DSU guidance. The modelling of independent survival curves was chosen as the appropriate methodology as outlined in Sections 5.3.2 to 5.3.4 below. The final choice of the parametric survival model adopted for the base-case analysis was therefore made with consideration for statistical fit within the period when patient-level data were available (as per AIC/BIC values), visual inspection of fit versus the Kaplan Meier curves and long-term clinical plausibility of the extrapolated models.

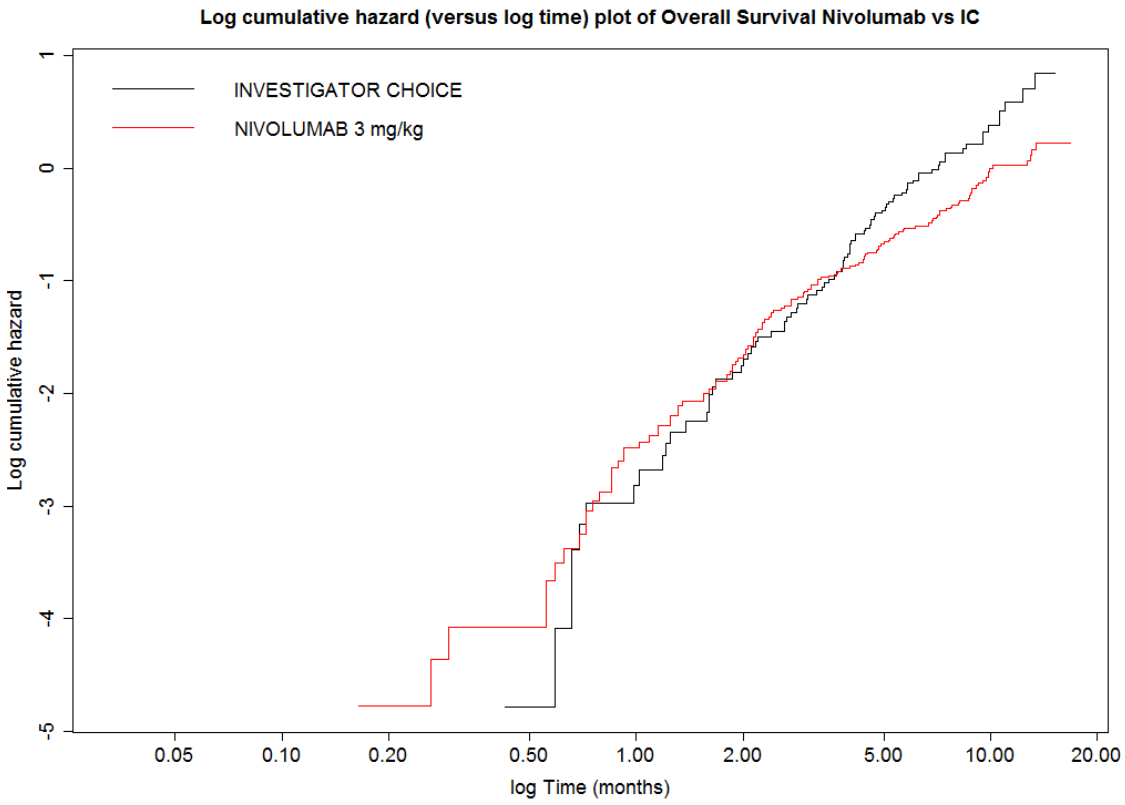
Clinical plausibility of extrapolated parametric models was based on expert clinical opinion and comparison with clinical trial data for nivolumab from other indications over a longer follow-up than CheckMate 141 (see Section 5.3.2.1). In particular, trials of longer follow-up in patients with advanced, squamous NSCLC were used for the validation of modelled outcomes as this indication is considered suitable for comparison with SCCHN due to similarities in tumour histology and patient characteristics (e.g. age, smoking status – see Appendix 5). Clinical feedback sought as part of model development supported the use of data for nivolumab from squamous NSCLC as validation for longer-term survival outcomes in the absence of any other data.[7] The US Surveillance, Epidemiology, and End Result Program (SEER) and the UK Oxford Cancer Intelligence Unit (OCIU, 2011) were also considered as data sources for validation of long-term extrapolations. However, due to difficulties in identifying an analogous population to that of the CheckMate 141 trial, within these data (neither source reported survival rates for patients with platinum-refractory R/M SCCHN, specifically), these sources were not considered for validation of modelled outcomes.[117-119]

Finally, the DSU guidance notes that when fitting independent parametric models, the same statistical distribution should be used in each treatment arm unless there is substantial justification for different distributions – this guidance was also considered in the choice of the parametric distribution adopted for the base case analysis.

5.3.2 Extrapolation models for OS

Figure 23 shows the log cumulative hazard plot for OS based on the latest available data cut for OS from CheckMate 141. Due to the fact that the curves are not parallel and can be seen to overlap each other at several time points before separating from approximately 4 months on, it is evident that an assumption of proportional hazards does not hold. Given this, and the availability of patient-level data for both the nivolumab arm and IC arm of CheckMate 141, the fitting of independent parametric survival distributions for OS to nivolumab and the comparators was pursued in line with points 1 and 2 in the guidance summary above.

Figure 23: log cumulative hazard plot of OS for nivolumab versus IC



Abbreviations: IC: investigator's choice;

The full range of parametric survival distributions specified in the DSU were explored as independent models for OS of nivolumab and comparator efficacy. In addition to this, spline-based models were explored. These represent flexible models that segment the curve into different polynomial functions based on a number of knots, where it is implicitly assumed that the number of knots represents the number of potential heterogeneous subgroups of patients. Spline-based models have been presented and described in previous submissions for nivolumab and are recommended by the NICE DSU guidance document on parametric survival analysis as an alternative to standard parametric and piecewise modelling approaches.[24] Previous feedback from health economists and clinicians has determined that when using these flexible models, the model should balance goodness of fit alongside clinical plausibility. In particular, the nature of spline methods means that whilst these models can be made to produce a good visual fit to the trial data this does not necessarily mean that there is reduced uncertainty in the extrapolation of the curve. Spline based models can increase in complexity based on the number of intermediate knots defined within the distribution and the use of spline models should represent a balance

between the added benefit of the increased flexibility of the method and the need for this increased complexity. A previous ERG has suggested that where simpler parametric models are demonstrated to provide sufficient fit to the data these may be preferable to more complicated spline models.[120] Given this, only 1- and 2-knot spline models were explored.

Table 25 summarises the AIC/BIC values for the variety of independent parametric distributions explored for OS for nivolumab and for IC. In terms of statistical fit, it is evident that the lognormal distribution provides the best statistical fit to the data for both the nivolumab IC arms of CheckMate 141. Of the spline models, the 1-spline hazard and 1-spline normal models were the best fitting in both arms.

Table 25: Summary of goodness-of-fit data for nivolumab OS models

Distribution	AIC	BIC
Exponential	900.0974	903.5781
Weibull	902.0810	909.0423
Gamma	901.8304	908.7917
Gompertz	900.6289	907.5901
Lognormal	892.7421	899.7033
Loglogistic	895.9007	902.8619
Generalised-gamma	894.7097	905.1516
Spline models:		
1-spline hazard	894.5193	904.9612
1-spline odds	895.1440	905.5859
1-spline normal	894.6624	905.1043
2-spline hazard	896.0227	909.9452
2-spline odds	896.2647	910.1873
2-spline normal	896.6253	910.5478

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

Table 26: Summary of goodness-of-fit data for IC of therapy OS models

Distribution	AIC	BIC
Exponential	510.9038	513.6996
Weibull	502.4814	508.0729
Gamma	500.7490	506.3406
Gompertz	508.4971	514.0887
Lognormal	500.0680	505.6596
Loglogistic	500.2528	505.8444
Generalised-gamma	501.2385	509.6259
Spline models:		
1-spline hazard	501.6248	510.0121
1-spline odds	502.2196	510.6070
1-spline normal	501.0333	509.4206
2-spline hazard	503.5248	514.7080
2-spline odds	504.0737	515.2568
2-spline normal	503.0647	514.2479

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

Given that the spline models do not provide a better statistical fit compared to simpler distributions (e.g. lognormal), and provide a similar fit to other simpler distributions (e.g. loglogistic and generalised-gamma), it was considered that the added complexity of these models was not justified. As such, these models were excluded from further consideration for the modelling of OS. The long-term OS extrapolations for nivolumab and IC with all other parametric distributions are provided in Figure 24 and Figure 25, respectively.

Feedback from previous Evidence Review Group critiques of analyses submitted to NICE for the appraisal of nivolumab in other cancer indications was also considered.[19, 20] Accordingly, consideration was given to how the long-term survival estimates related to the other clinical parameters and also to age-matched general population mortality in order to ensure that no logical inconsistencies were encountered (e.g. the proportion of patients still on-treatment or progression-free should not exceed the proportion of patients alive in the cohort).

From the below figures, it is clear that for nivolumab the extrapolations from the Weibull, Gamma and exponential distributions model a sharper decrease in survival and a lower proportion of survivors over the extrapolated periods. These models were seen to rank poorly in terms of fit to the nivolumab trial data compared to the lognormal model but were considered further to characterise the most pessimistic scenario with regards to OS. With the exception of the Gompertz model, all other distributions produced curves that were consistent with one another on visual inspection (see figures below). The mean OS values predicted by these different parametric models are provided in Table 27. These indicate that the mean OS in both the nivolumab arm and the IC arm is sensitive to choice of parametric distribution for OS. Therefore, the choice of an OS distribution that predicted a) a more pessimistic and b) a more optimistic OS with nivolumab were explored in scenario analyses to characterise the possible range of results. The distribution chosen for the pessimistic scenario was the Weibull distribution (see Scenario 4 in Section 5.8.3), based on the considerations noted above. For the optimistic scenario, a 1-

spline odds distribution was chosen (see Scenario 5 in Section 5.8.3). Although spline models were not considered in the base case for the reasons outlined above, this spline model was considered appropriate to use as the distribution for a scenario analysis exploring the most optimistic estimates for mean OS with nivolumab.

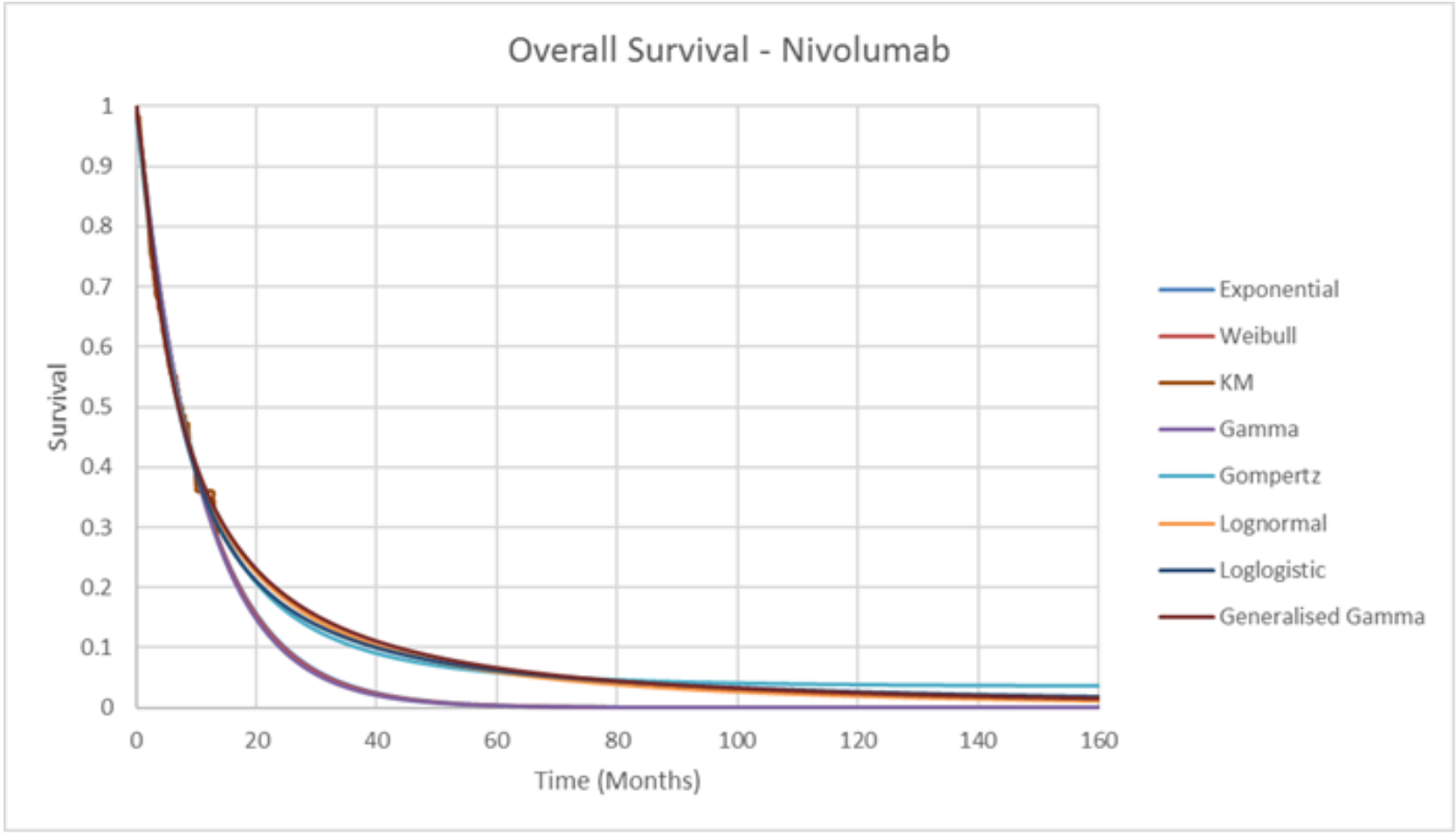
Table 27: Summary of predicted mean OS values for nivolumab and investigator's choice

Distribution	Predicted mean OS - nivolumab	Predicted mean OS - IC
Exponential	11.2	7.8
Weibull	11.2	7.0
Gamma	11.0	7.1
Gompertz	21.0	6.9
Lognormal	17.7	8.4
Loglogistic	18.7	9.1
Generalised-gamma	18.6	7.6

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: IC: investigator's choice; OS: overall survival.

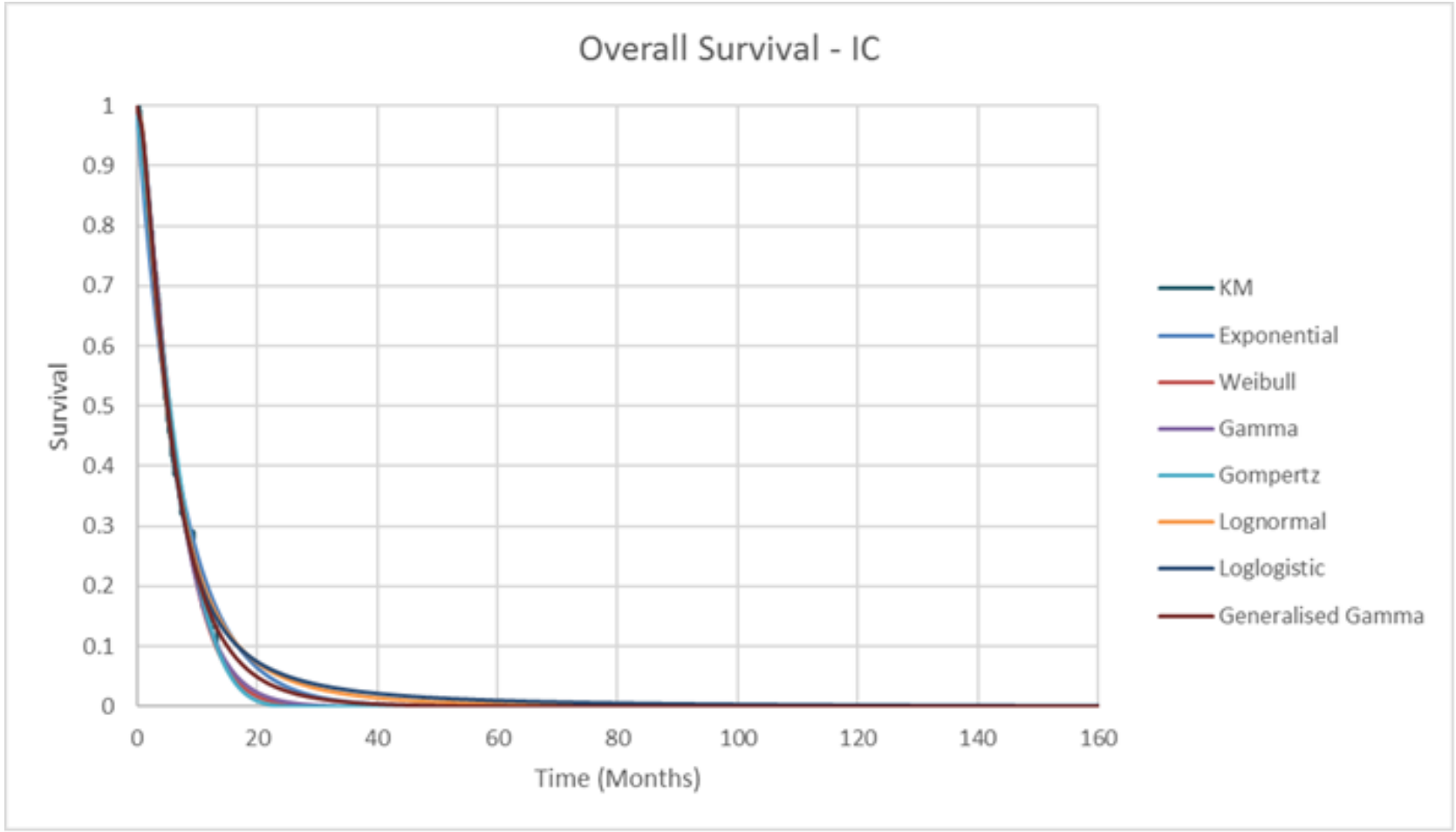
Figure 24: Long-term OS extrapolation of non-spline parametric models - nivolumab



Spline-based models are excluded from this figure (see explanation in the text)

Abbreviations: KM: Kaplan Meier; OS: overall survival.

Figure 25: Long-term OS extrapolation of non-spline parametric models - IC



Abbreviations: IC: investigator's choice; KM: Kaplan Meier; OS: overall survival.

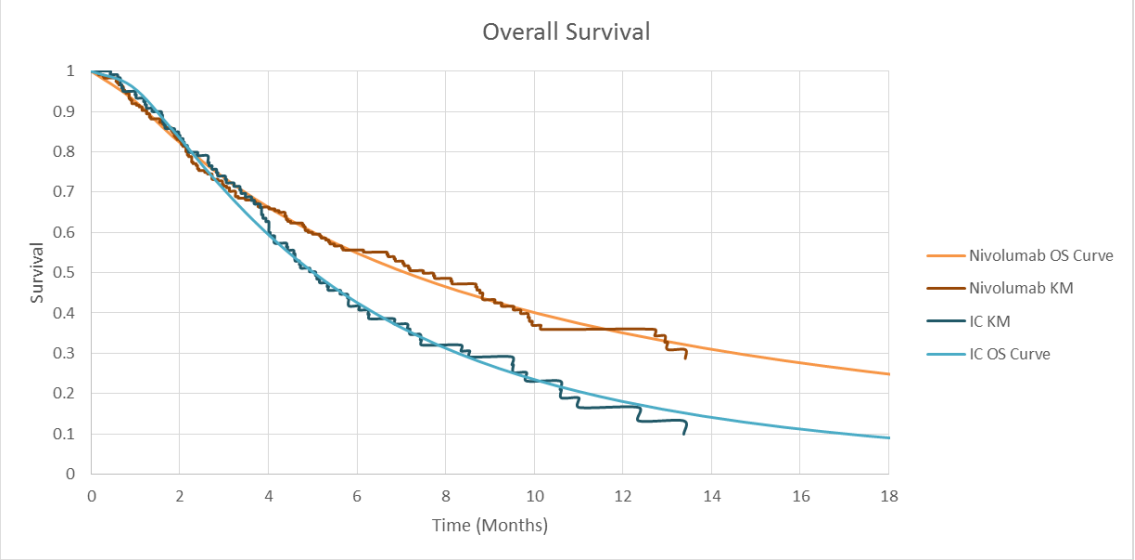
5.3.2.1 Selection of the base-case OS parametric distribution

Determination of the base case parametric model for OS was based on consideration of the curve fit to the trial data (in terms of AIC/BIC values and visual inspection), a preference for using the same parametric model for both nivolumab and comparator therapies as per the recommendation in NICE DSU Technical Support Document (TSD) 14, consistency between long term estimates of OS, PFS and TTD as well as age-matched general population mortality rates, and validation against available long-term data.

Based on AIC/BIC values (see Table 25 and Table 26), the lognormal was the best fitting curve for both the nivolumab and IC arms of CheckMate 141. Visual inspection also indicated a satisfactory fit to the trial data (see Figure 26). Moreover, the lognormal produced estimates of OS that did not generate inconsistency with the long-term estimates of PFS and TTD. Additionally, the resultant probability of mortality within the next year remained higher than for the general population at all time points within the 20-year time horizon, as may be expected for patients with R/M SCCHN, and without explicitly modelling the possibility of an immuno-oncology effect observed in other indications.[33, 34]

A more pessimistic distribution (the Weibull) for OS with nivolumab was also explored in order to explore the impact of the choice of OS distribution on cost-effectiveness. However, it should be noted that the choice of the Weibull distribution for OS produced OS estimates that fell below the base case PFS and TTD curves at later time points. This is fundamentally implausible as patients cannot have died and still be incurring treatment costs. Additionally, for reasons discussed further below, the Weibull distribution was not considered to be a plausible choice for the base case analysis.

Figure 26: Plot of lognormal curve fit to Kaplan-Meier data for nivolumab and IC (OS)



Abbreviations: IC: investigator's choice; KM: Kaplan Meier; OS: overall survival.

Validation of the nivolumab arm

No longer-term OS data (than from the pivotal CheckMate 141 trial) were identified by the clinical SLR for the use of nivolumab in platinum-refractory R/M SCCHN (see Section 4.1). The CheckMate 141 trial was initiated based on preclinical data and results from CheckMate 003: a phase I dose escalation study that included patients with select previously-treated, advanced

solid tumours (not including SCCHN). This study demonstrated the ability of nivolumab to induce responses at estimated rates that equal or surpass those of active controls in a spectrum of solid tumours.[14]

In the absence of longer-term trial data, clinical expert opinion was sought as to the long-term OS estimates that may be expected with nivolumab for SCCHN. Given the lack of longer follow-up from CheckMate 141 or earlier phase data, clinical experts suggested that long-term survival data for nivolumab in other indications could be used to estimate the potential long-term benefit of nivolumab in SCCHN.[7] Squamous NSCLC was highlighted as being the most relevant in terms of the similarity between indications in terms of tumour histology, patient characteristics (e.g. age, smoking status – see Appendix 5 for a comparison of the eligibility criteria and baseline characteristics between CheckMate 141 and advanced squamous NSCLC nivolumab trials) and prognosis (patients in the comparator arm of CheckMate 017, docetaxel 75 mg/m^2 Q3W, had a median OS of 6.0 months).[7, 105] Specifically, nivolumab monotherapy has been investigated as a treatment for squamous NSCLC in the phase III RCT CheckMate 017 and the single-arm CheckMate 063 trial, both of which included patients with advanced, platinum-refractory squamous NSCLC, and also in the dose-ranging CheckMate 003 phase I trial, which included multiple solid tumour types, including squamous NSCLC.[10, 106]

Data from these three trials are presented in Table 28 alongside model estimates of OS from the base case analysis and 1-year survival rates from CheckMate 141.

Table 28: Absolute OS estimates for nivolumab from clinical trials in advanced squamous NSCLC compared with trial data and extrapolations from CheckMate 141

Data source	Survival curve	Proportion alive, %				
		1 year	1.5 years	2 years	3 years	4 years
Nivolumab						
Model estimates for OS	Lognormal (base case)	35.2%	25.5%	18.8%	11.9%	8.2%
	Weibull (pessimistic)	32.8%	19.5%	10.6%	3.4%	1.1%
	1-spline odds (optimistic)	36.0%	27.3%	21.2%	14.9%	11.4%
CheckMate 141 (R/M SCCHN)	Nivolumab OS	36.0%	-	-	-	-
CheckMate 017 (squamous NSCLC)	Nivolumab OS	42%	28%	23%	-	-
CheckMate 063 (squamous NSCLC)	Nivolumab OS	39%	27%	-	-	-
CheckMate 003 (squamous NSCLC)	Nivolumab OS	49%	-	35%	28%	-

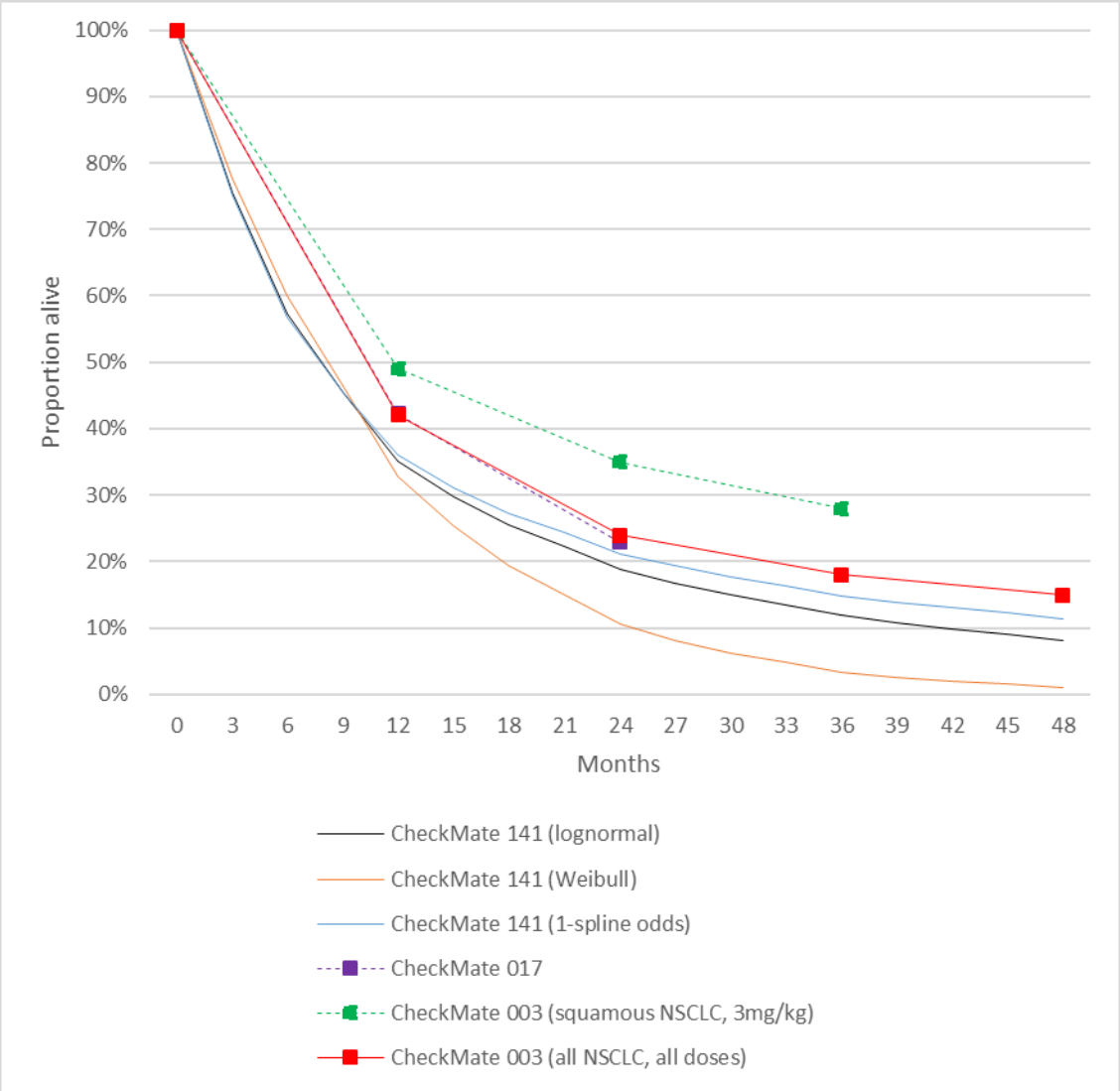
CheckMate 017 = phase III trial of nivolumab 3 mg/kg Q2W (n=135) versus docetaxel 75 mg/m^2 Q3W (n=137) in patients with advanced, platinum-refractory, squamous NSCLC.[105]
CheckMate 063 = single-arm phase II trial of nivolumab 3 mg/kg Q2W (n=117) in patients with advanced, platinum-refractory, squamous NSCLC.[121]
CheckMate 003 = dose-ranging phase I trial of nivolumab in multiple tumour types, including patients with advanced, squamous NSCLC treated with nivolumab 3 mg/kg Q2W (n=18)[106]

Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival; Q2W: once every 2 weeks; Q3W: once every three weeks; R/M: recurrent or metastatic; SCCHN: squamous cell carcinoma of the head and neck.

Source: Gillison *et al.* (2016)[8] for CheckMate 141; Ramalingam *et al.* (2016)[10] for CheckMate 017 and CheckMate 063 up to 18 months; Borghaei *et al.* (2016) for CheckMate 017 at 2-years;[122] Gettinger *et al.* (2015)[106] for CheckMate 003.

As shown in Table 28, data for patients receiving nivolumab 3 mg/kg are available up to 1.5 years, 2 years and 3 years for CheckMate 063, CheckMate 017 and the population of squamous NSCLC patients who received nivolumab 3 mg/kg in CheckMate 003, respectively. Data at an even later time point of 4 years is available from the CheckMate 003 study when considering all NSCLC patients (i.e. squamous and non-squamous) and all dose levels of nivolumab (i.e. not only the 3 mg/kg dose) (not shown in Table 28). In Figure 27, the absolute survival estimates with nivolumab from each of these trials are presented alongside the absolute survival estimates predicted by the economic model for the base case choice of survival distribution (lognormal) and also the pessimistic (Weibull) and optimistic (1-spline odds) distributions selected for scenario analyses (see Section 5.8.3). This analysis found that the absolute survival estimates with nivolumab in squamous NSCLC were similar to or greater than those predicted by either the lognormal OS curve or 1-spline odds OS curve. In contrast, the Weibull distribution predicted OS estimates over a period of up to 4 years that were considerably lower than have been observed in trials of nivolumab in NSCLC.

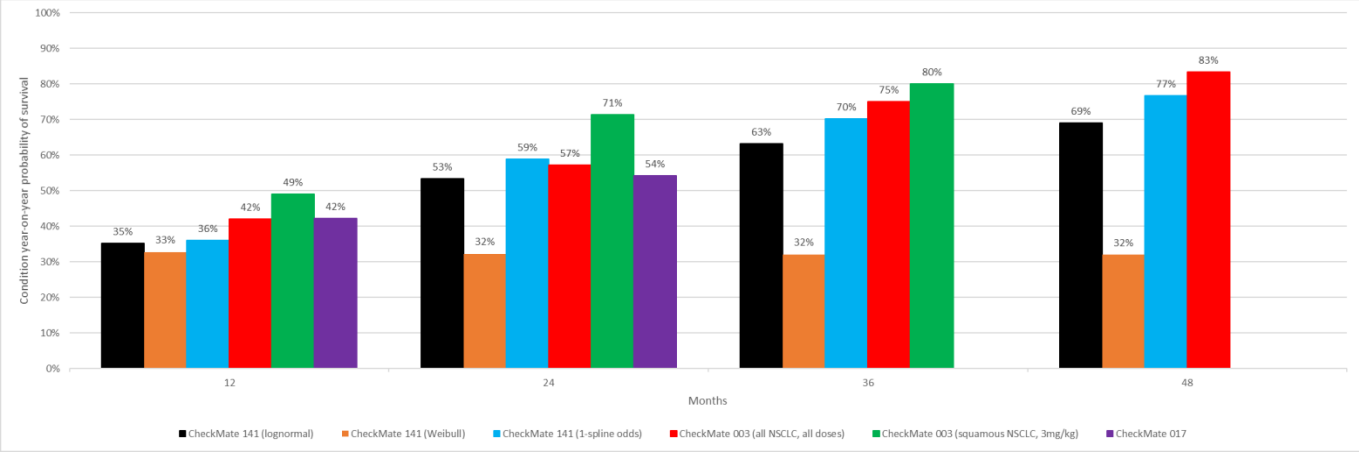
Figure 27: Absolute OS estimates for nivolumab from clinical trials in advanced squamous NSCLC compared with extrapolations from CheckMate 141



Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival.

There are limitations in assuming that absolute survival estimates are comparable across different indications; an analysis was therefore also conducted to consider the conditional year-on-year estimates of survival with nivolumab from this long-term data. These conditional estimates represent the proportion of patients who survived to year x, given that they were alive at year x-1 (for example, if 35.17% of patients were alive at year 1 and 18.76% of patients at year 2, the 2-year conditional survival estimate would be 18.76%/35.17% = 53.34%). Conditional estimates may be a more useful comparison as they take into account the potential inherent differences in absolute survival between different indications. The conditional survival estimates for the trials providing OS data of 2 years or more for nivolumab are presented in Figure 28 (hence the exclusion of CheckMate 063 from this analysis). Similar to the estimates of absolute survival, this analysis found that the conditional year-on-year survival predicted by the base case lognormal distribution was relatively well aligned to the conditional survival estimates that have been observed with nivolumab in trials of nivolumab in squamous NSCLC and NSCLC more broadly. In contrast, the Weibull distribution did not provide conditional survival estimates that were well matched.

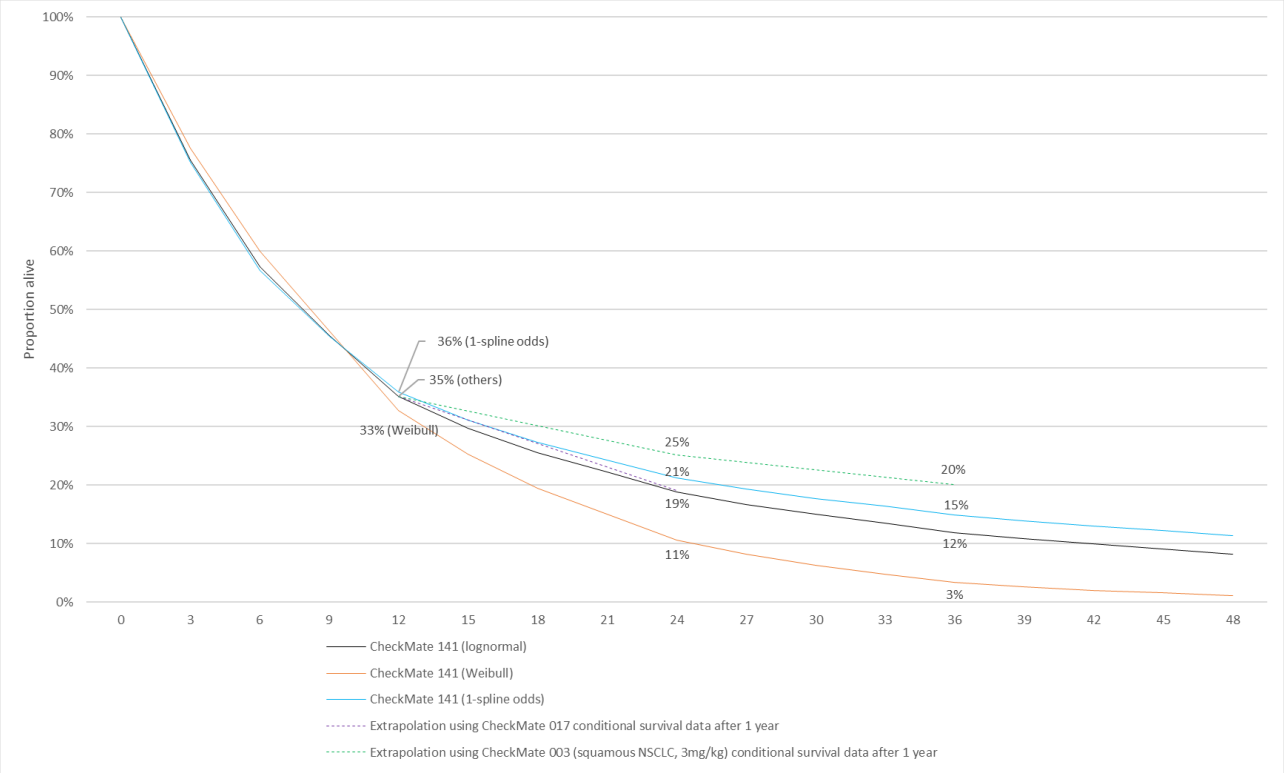
Figure 28: Conditional year-on-year OS estimates for nivolumab from clinical trials in advanced squamous NSCLC compared with extrapolations from CheckMate 141



Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival.

A final validation exercise made use of the conditional survival estimates provided by the CheckMate 017 and CheckMate 003 trials and applied these to the 1-year absolute survival estimates predicted by the base case lognormal curve. This analysis makes use of the modelled data from the indication of R/M SCCHN specifically up to the time point for which this data is available in the CheckMate 141 study. It then extrapolates estimated absolute survival from this point based on observed longer-term conditional survival rates from trials of nivolumab in the NSCLC population. For this analysis, the all NSCLC population from CheckMate 003 was excluded as the squamous population from this study represents the most relevant comparison. The results of this analysis are presented in Figure 29.

Figure 29: Comparison of modelled survival estimates with conditional survival-based extrapolations from NSCLC trials of nivolumab



Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival.

In this analysis, extrapolated estimates up to 2 years from CheckMate 017 were seen to align very closely to those predicted by the lognormal curve (both 19% at 2 years). The extrapolation using conditional survival estimates from the squamous NSCLC population of CheckMate 003 who were treated with 3 mg/kg nivolumab predicted overall survival slightly in excess of either the lognormal or 1-spline odds curves. The Weibull curve consistently predicted overall survival with nivolumab well below the extrapolated estimates from the CheckMate 017 and CheckMate 003 trials over the period for which comparative data was available.

Validation of the investigator's choice arm

As noted previously, the US SEER and the UK OCIU were considered as data sources for validation of long-term extrapolations for currently-available therapies. However, due to difficulties in identifying an analogous population to that of the CheckMate 141 trial, within these data (with neither source reporting survival rates for patients with platinum-refractory R/M SCCHN, specifically) these sources were not considered for validation of modelled outcomes.[117-119] For example, the 5-year relative survival rates reported by SEER for patients with metastasised cancer of the larynx (35.1%) and metastasised cancer of the oral cavity or pharynx (38.0%) are considerably higher than those expected based on expert clinical opinion, suggesting the populations considered in the SEER data available cannot be considered representative of patients with R/M SCCHN who have progressed on platinum therapy in clinical practice.[117, 118]

The clinical SLR identified one non-randomised study presenting survival estimates for patients receiving treatment for platinum-refractory R/M SCCHN.[5] This was a retrospective medical record study of patterns and care and healthcare resource use in UK patients with metastatic SCCHN who had received at least three lines of prior systemic therapy. The information on this

study was limited to a congress poster.[5] This study reported that at least 64.6% of included patients had previously received platinum-based therapy as a first-line therapy and presented OS estimates for patients in the study who received third-line therapy.[5] The median OS reported for these third-line patients was 8.8 months (95% CI 8.0, 10.4), which is much longer than would be expected based on expert clinical opinion and the evidence from CheckMate 141.[5] This may be the result of the study design, which required patients to have had at least three lines of treatment in the metastatic setting, thereby selecting a patient group which would have had a better prognosis than normally expected. Again, as this is a different patient population to the CheckMate 141 trial population it was not considered an appropriate source for validation of long-term survival estimates for the IC arm, but is highlighted here for the purpose of transparency.

Expert clinical opinion gathered at an international advisory board was that 4-year OS in current clinical practice for the relevant patient population is 1–2%.[6] Expert opinion of UK clinicians provided in one-on-one interviews suggested that 10–20% of patients would be alive at 1 year and 5% alive at 2 years in current clinical practice.[7] In the absence of other data, these estimates were used for comparison with estimates from the chosen base case distribution for OS. Data from the sources summarised above are presented in Table 29, alongside the model estimates using the lognormal distribution for OS. This validation exercise found the lognormal distribution to produce survival estimates that were well aligned with the data available for validation.

Table 29: Overall survival estimates for the IC arm based on clinical opinion compared with trial data and extrapolations from CheckMate 141

Data source	Survival curve	Proportion alive, %			
		1 year	2 years	3 years	4 years
Investigator's Choice					
Model estimates for OS	Lognormal (base case)	18.1%	5.1%	2.0%	0.9%
	Weibull (pessimistic)	13.4%	0.6%	0.0%	0.0%
	1-spline odds (optimistic)	17.0%	5.3%	2.5%	1.5%
CheckMate 141	IC of therapy OS	16.6%	-	-	-
Clinical opinion	Current clinical practice	10–20%	5%	-	1-2%

Abbreviations: IC: investigator's choice; OS: overall survival.
Source: Gillison *et al.* (2016)[8]

Summary of extrapolation models for OS

The lognormal distribution was therefore selected as the base case distribution for both nivolumab and comparator therapies. In summary, the reasons for this selection were that:

- Consistent with DSU guidance, there was a preference to use the same distribution to model both nivolumab and comparator efficacy
- The lognormal distribution had the best statistical fit to trial data by both AIC and BIC and for both the nivolumab and IC arms
- The lognormal distribution was judged to have good visual fit on inspection in both arms

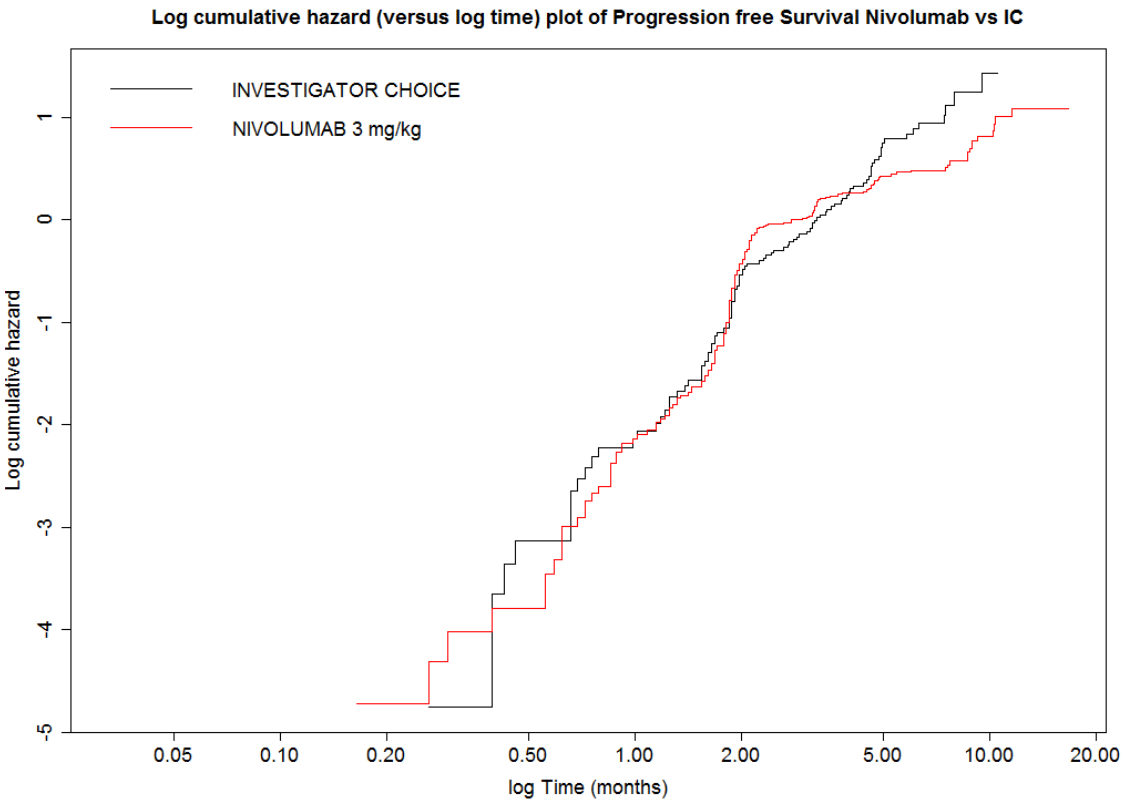
- The lognormal distribution provided OS estimates which did not produce any logical inconsistencies compared to PFS and TTD (base case), and the age-matched general population mortality rate
- Extrapolations with the lognormal distribution generated estimates for nivolumab that were well aligned to evidence for survival with nivolumab in squamous NSCLC and estimates for IC that aligned with expert clinical opinion regarding OS at 1, 2 and 4 years

5.3.3 Extrapolation models for PFS

Consideration of the approach for modelling of PFS proceeded as described for OS above.

Figure 30 shows the log cumulative hazard plot for PFS based on the latest available data cut for PFS from CheckMate 141. Due to the fact that the curves are not parallel and can be seen to overlap each other at several time points before separating from approximately 5 months onwards, it is evident that an assumption of proportional hazards does not hold. Given this, and the availability of patient-level data, the fitting of independent parametric survival distributions for PFS to nivolumab and the comparators was pursued.

Figure 30: log cumulative hazard plot of PFS for nivolumab versus IC



Abbreviations: IC: investigator's choice; KM: Kaplan Meier; PFS: progression-free survival.

As for OS, the full range of parametric survival distributions specified in the DSU were explored as independent models for PFS of nivolumab and comparator efficacy, in addition to spline-based models. Table 30 summarises the AIC/BIC values for the variety of independent parametric distributions explored for PFS for nivolumab and for IC. For nivolumab, the best-fitting models were seen to be spline models (notably the 2-spline odds and 2-spline normal). Of the non-spline models, the loglogistic was the best fitting, followed by the generalised gamma and

lognormal distributions. For IC, the best fitting curve was the loglogistic, followed by the generalised gamma, lognormal and 1-spline hazard and 1-spline normal models.

Given that there was no single distribution that was clearly the best fitting by AIC/BIC to both the nivolumab and IC data, and that the preference was to use the same parametric distribution in both arms, a number of potential distributions were taken forwards for further visual inspection and consideration for the base case distribution. These were the 2-spline odds (as the best fitting for nivolumab), the loglogistic (as best fitting for the IC arm) and the generalised gamma and lognormal (as well fitting for both arms).

Table 30: Summary of goodness-of-fit data for nivolumab PFS models

Distribution	AIC	BIC
Exponential	893.6523	897.1330
Weibull	888.9784	895.9397
Gamma	879.2260	886.1873
Gompertz	894.0397	901.0010
Lognormal	842.7126	849.6739
Loglogistic	835.4127	842.3740
Generalised-gamma	841.9505	852.3924
Spline models:		
1-spline hazard	821.8261	832.2680
1-spline odds	822.1553	832.5972
1-spline normal	839.8230	850.2649
2-spline hazard	814.7205	828.6430
2-spline odds	803.9737	817.8963
2-spline normal	803.6091	817.5317

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

Table 31: Summary of goodness-of-fit data for IC of therapy PFS models

Distribution	AIC	BIC
Exponential	449.1393	451.9351
Weibull	424.9348	430.5264
Gamma	420.7156	426.3072
Gompertz	439.3768	444.9683
Lognormal	421.9280	427.5195
Loglogistic	420.7133	426.3049
Generalised-gamma	421.4421	429.8295
Spline models:		
1-spline hazard	421.3533	429.7407
1-spline odds	422.1099	430.4973
1-spline normal	421.2209	429.6083
2-spline hazard	423.3935	434.5767
2-spline odds	423.6595	434.8427
2-spline normal	423.0645	434.2477

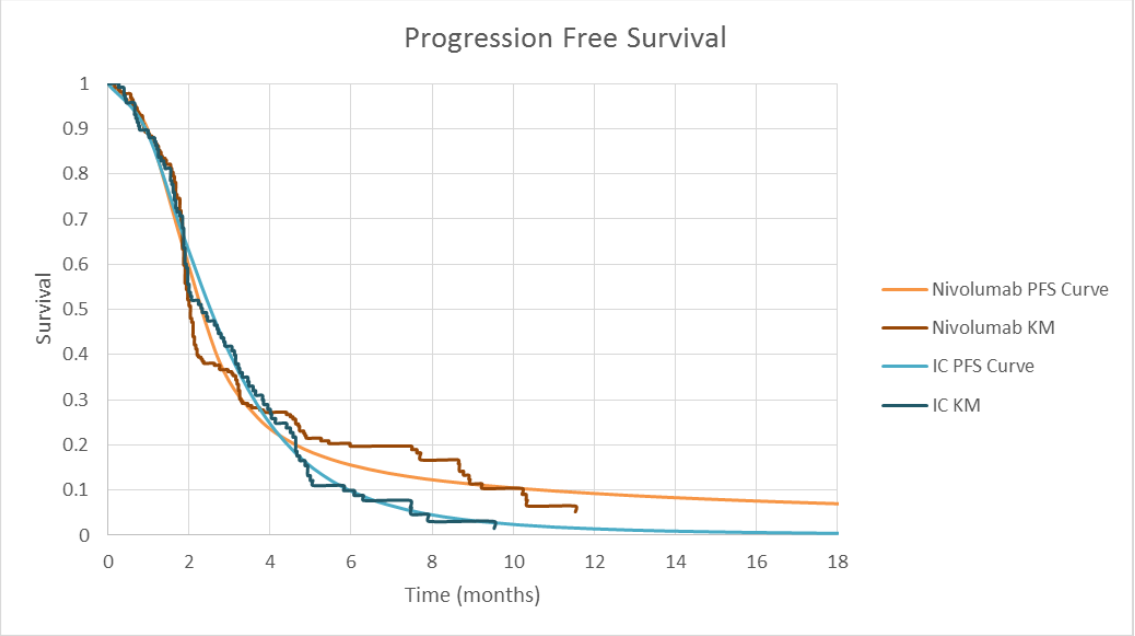
The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

5.3.3.1 Selection of the base-case PFS parametric distribution

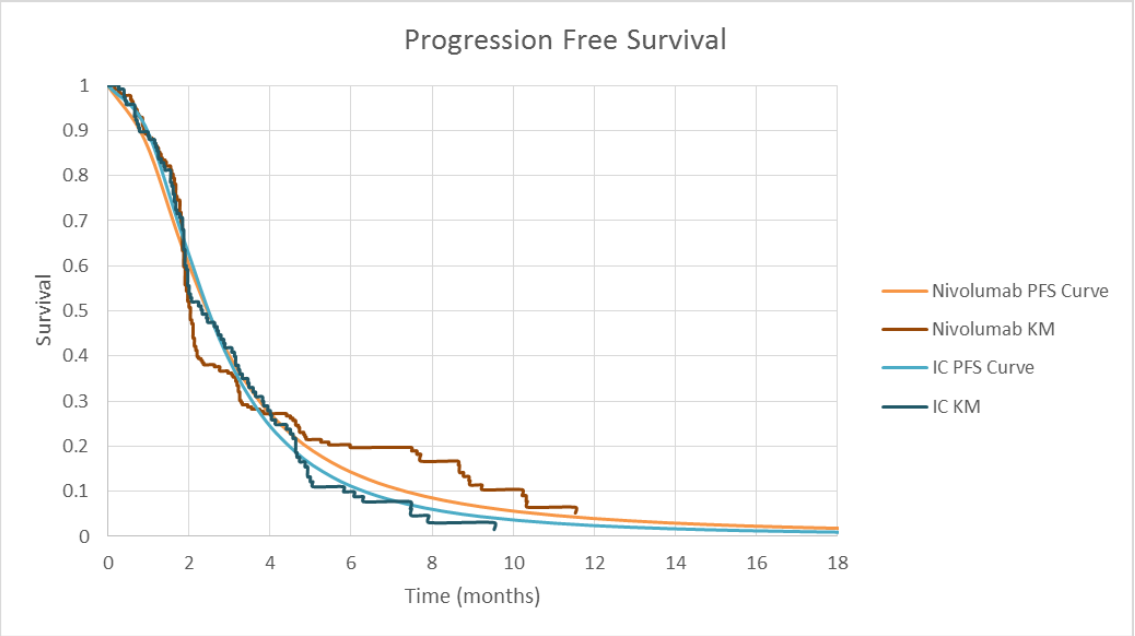
Fits to the CheckMate 141 Kaplan-Meier data for both nivolumab and IC are presented in figures below for each distribution taken forwards for consideration as the base case distribution. By visual inspection none of the curves were seen to have particularly strong fit to the nivolumab Kaplan-Meier data, with all parametric distributions tending to lie above the Kaplan-Meier curves in the first few months before falling beneath this until at least around 9 months. The 2-spline odds and generalised gamma curves appeared to have better fit to the nivolumab data than the loglogistic or lognormal curves. For the IC data, fit was generally better and again visual inspection revealed a preference for the generalised gamma over the loglogistic or lognormal.

Figure 31: Plot of 2-spline odds curve fit to Kaplan-Meier data for nivolumab and IC (PFS)



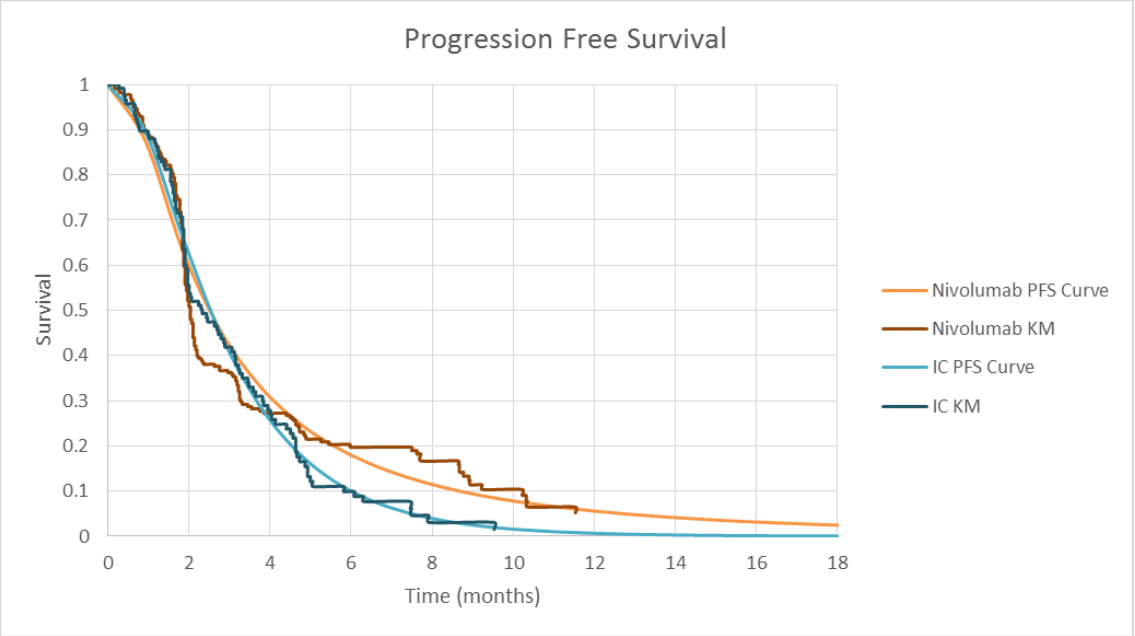
Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 32: Plot of loglogistic curve fit to Kaplan-Meier data for nivolumab and IC (PFS)



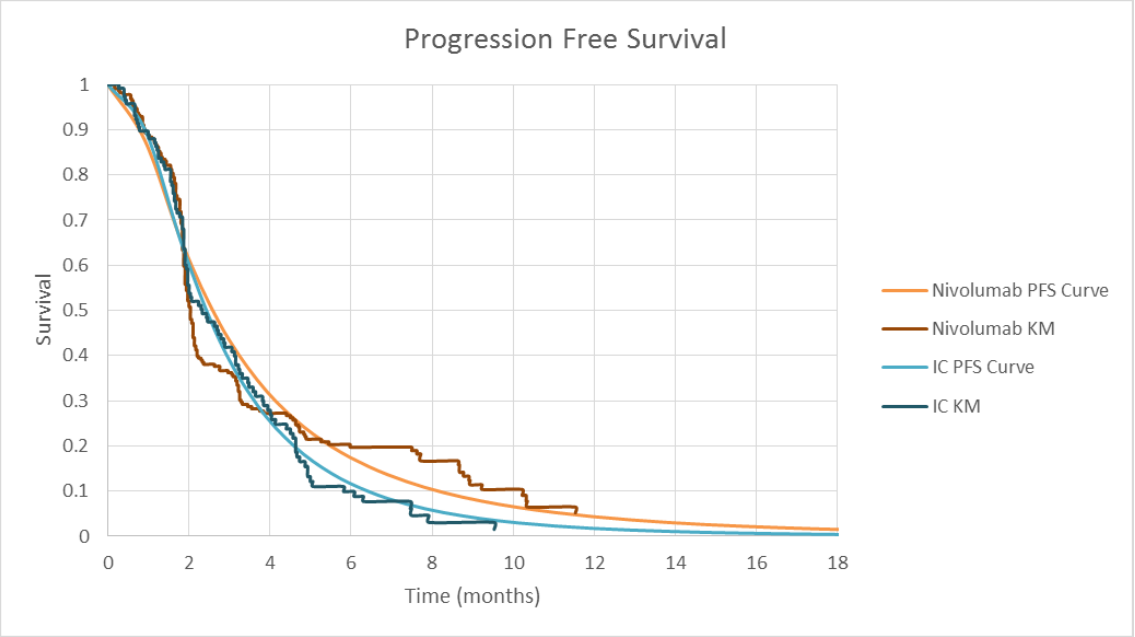
Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 33: Plot of generalised gamma curve fit to Kaplan-Meier data for nivolumab and IC (PFS)



Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 34: Plot of lognormal curve fit to Kaplan-Meier data for nivolumab and IC (PFS)



Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; PFS: progression-free survival.

In addition to visual fit to the Kaplan-Meier data, figures for long-term extrapolation (see Figure 35 for nivolumab and Figure 36 for IC) and mean PFS values (see Table 32) predicted by each parametric distribution were also considered to inform the decision as to the base case distribution.

As noted in Section 5.2, PFS was used to determine the proportion of patients in the *progression-free* and *progressed disease* health states. However, treatment duration in the model was based on TTD from CheckMate 141, rather than PFS – as such, the use of curves that appear to underestimate PFS for nivolumab on visual inspection versus Kaplan-Meier data is

likely to provide a conservative estimate of the proportion of patients in the progression-free health state for nivolumab and does not affect the accrual of medication costs. Furthermore, as demonstrated in scenario analyses (see Scenarios 6–7 in Section 5.8.3), the ICERs for nivolumab versus comparators are not particularly sensitive to the choice of PFS distribution.

Table 32: Summary of predicted mean PFS values for nivolumab and IC

Distribution	Predicted mean PFS - nivolumab	Predicted mean PFS - IC
2-spline odds	9.2	3.7
Loglogistic	4.3	3.9
Generalised gamma	4.6	3.6
Lognormal	4.3	3.7

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: IC: investigator's choice; PFS: progression-free survival.

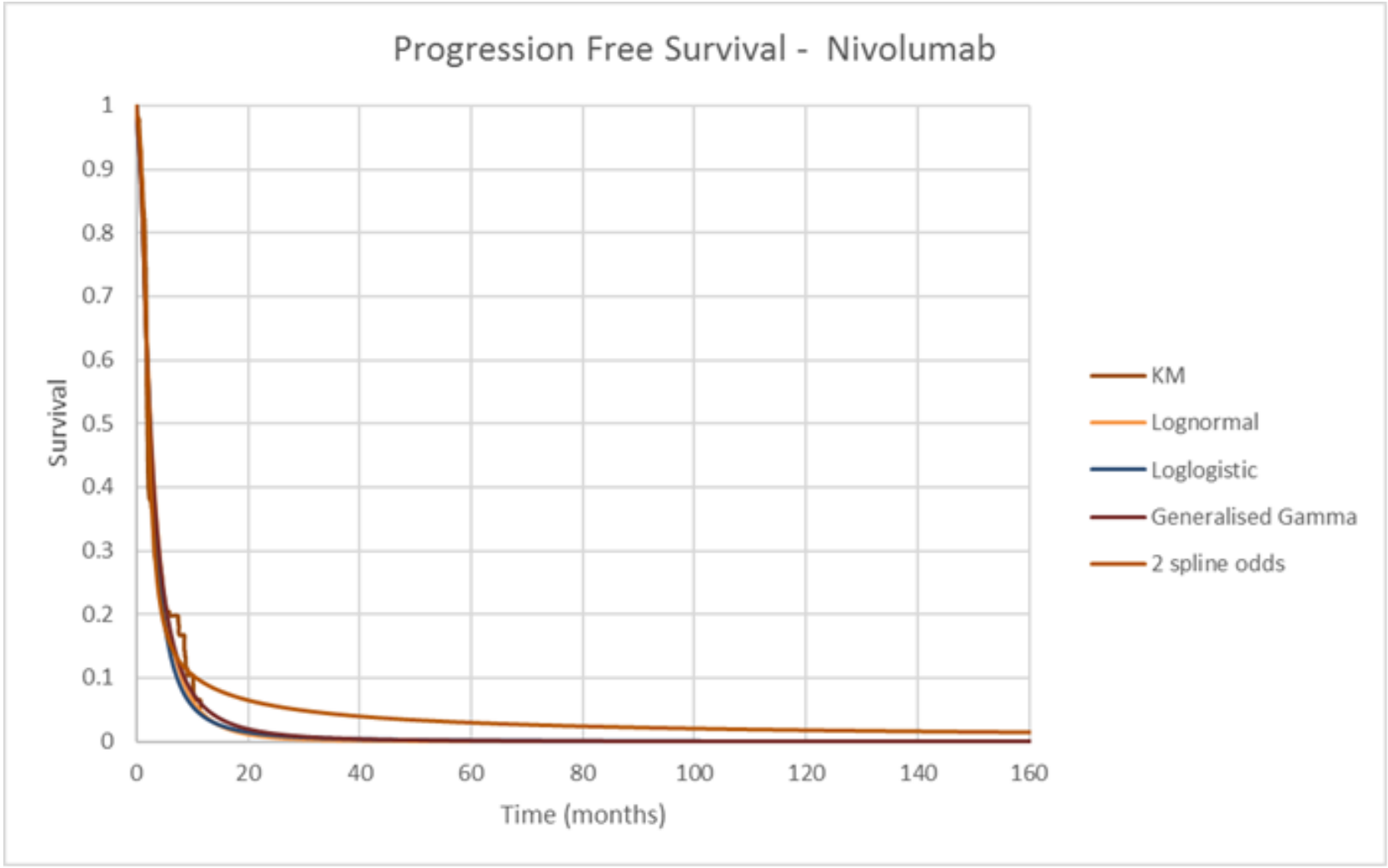
The choice of parametric distribution in the IC arm was seen not to influence mean PFS to any great extent. Furthermore, there was no clear difference in the shape of the long-term extrapolation between different distribution choices. For nivolumab, the choice of the distribution did impact on mean PFS and the shape of the 2-spline odds distribution was clearly associated with a more optimistic extrapolation of PFS with nivolumab (as were the other spline-based models), compared to other distributions. Notably, this long extrapolation of the nivolumab 2-spline odds PFS curve (see Figure 35) is driven by the latter portion of the nivolumab PFS Kaplan-Meier curve from CheckMate 141 (see Figure 11, Section 4.7.2) – a portion for which there were very few patients at risk.

The 2-spline odds distribution was considered inappropriate for the base case given that:

- The mean PFS estimates from the 2-spline odds curve for nivolumab was far greater than the non-spline distributions, and this was driven by small patient numbers in the tail of the Kaplan-Meier curve for nivolumab PFS
- Although a good statistical fit by AIC/BIC for the nivolumab arm, simpler models (lognormal, loglogistic, generalised gamma) were a better statistical fit for the IC arm and so the 2-spline odds model was discounted based on a preference for the same functional form for both arms

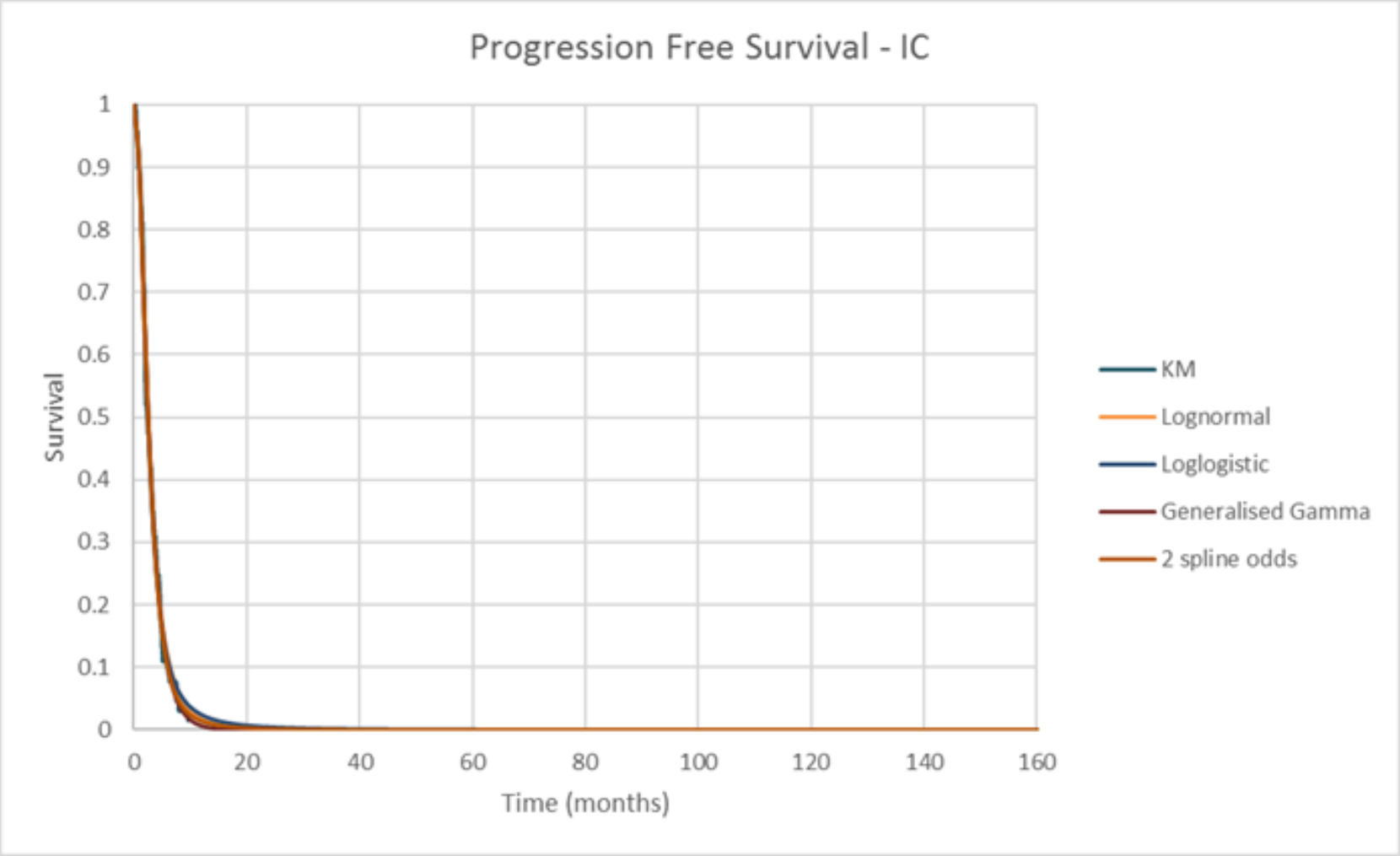
Of the loglogistic, lognormal and generalised-gamma, the loglogistic distribution had the best fit by AIC and BIC in both the nivolumab and IC arms. However, based on visual inspection the generalised-gamma appeared the more appropriate choice of curve compared to the loglogistic distribution; it appeared to match the Kaplan-Meier data for IC more closely, to over-predict Kaplan-Meier PFS data in the nivolumab arm to a similar degree at early time points and to under-predict Kaplan-Meier PFS data in the nivolumab arm to a lesser degree at later time points. Visual fit compared to the lognormal distribution was similar, though the generalised-gamma distribution perhaps appeared to match the Kaplan-Meier data for the IC arm more closely. The generalised-gamma distribution was therefore selected for the base case. The choice of distribution for PFS was tested in scenario analyses exploring distributions that provided pessimistic and optimistic estimates of PFS with nivolumab (see Scenarios 6–7 in Section 5.8.3).

Figure 35: Long-term PFS extrapolation of best-fitting parametric models - nivolumab



Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Figure 36: Long-term PFS extrapolation of best-fitting parametric models - IC

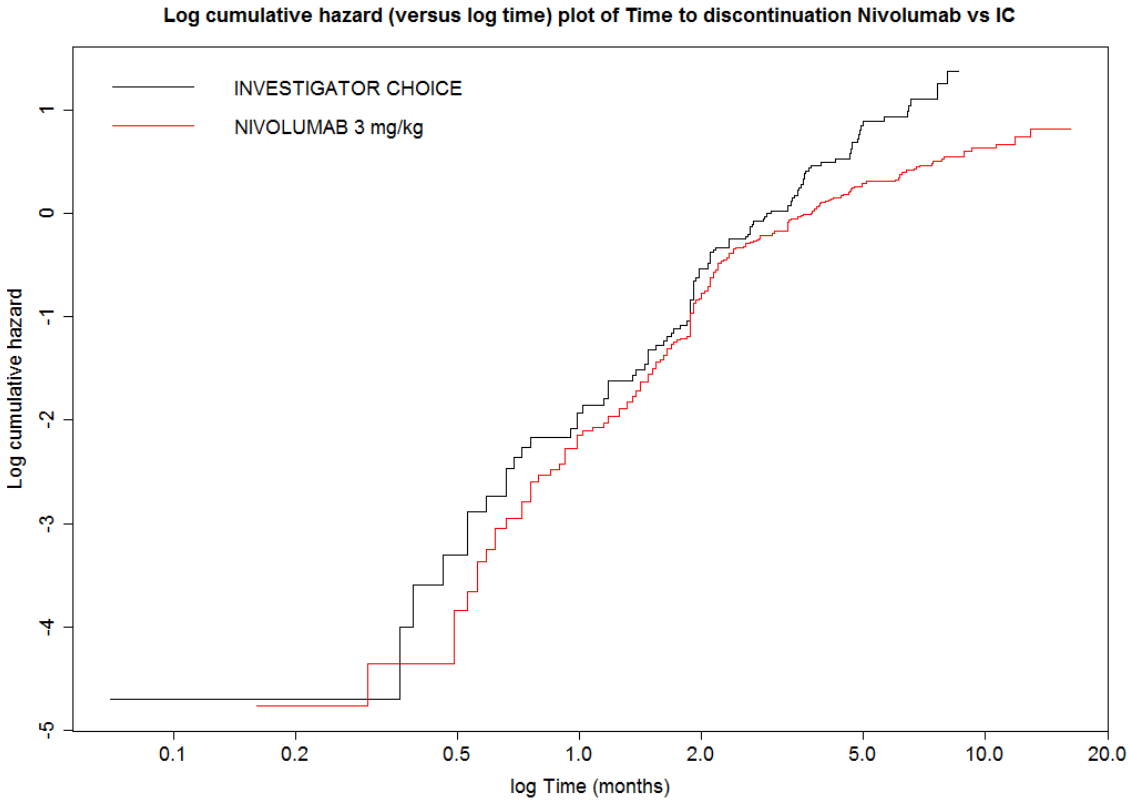


Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; PFS: progression-free survival.

5.3.4 Extrapolation models for TTD

Figure 37 provides the log cumulative hazard plot for TTD based on the latest available data cut from CheckMate 141. Due to the fact that the curves cross (at approximately 2.0 months) an assumption of proportional hazards does not appear to hold. With the availability of patient-level data for TTD, independent parametric distributions were explored for TTD.

Figure 37: log cumulative hazard plot of TTD for nivolumab versus IC



Abbreviations: IC: investigator's choice; TTD: time to discontinuation.

As for OS and PFS, the full range of parametric survival distributions specified in the DSU TSD were explored as independent models for PFS of nivolumab and comparator efficacy, in addition to spline-based models.

Table 33 summarises the AIC/BIC values for the variety of independent parametric distributions explored for TTD for nivolumab and for IC. For nivolumab, the best-fitting models were seen to be spline models (notably the 2-spline odds and 2-spline normal). Of the non-spline models, the loglogistic was the best fitting, followed by the generalised gamma. For IC, the best fitting curve was the gamma distribution followed by a number of other distributions that were similar in fit. As noted above for PFS, the extrapolations from the spline-based curves are influenced by the tail ends of the Kaplan-Meier plots. However, there is substantial uncertainty in the extrapolated tail because there are very few patients at risk towards the end of the Kaplan-Meier curve. In addition, as noted previously, where simpler models provide sufficient fit to the data these are likely to be preferable to spline-based models. Based on the above, and taking into account the strong preference for both nivolumab and comparator arms to be modelled with the same distribution and hence the need for reasonable fit for both nivolumab and the IC arm, the distributions considered for the base case were the 2-spline odds, 2-spline normal, generalised gamma and loglogistic distributions.

Table 33: Summary of goodness-of-fit data for nivolumab TTD models

Distribution	AIC	BIC
Exponential	987.4401	990.9040
Weibull	986.2668	993.1944
Gamma	979.6614	986.5891
Gompertz	985.2420	992.1697
Lognormal	943.0808	950.0085
Loglogistic	940.2247	947.1524
Generalised-gamma	941.1387	951.5302
Spline models:		
1-spline hazard	926.0282	936.4197
1-spline odds	926.9783	937.3698
1-spline normal	939.1030	949.4945
2-spline hazard	925.6786	939.5340
2-spline odds	922.8006	936.6559
2-spline normal	922.7013	936.5566

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; TTD: time to discontinuation.

Table 34: Summary of goodness-of-fit data for IC of therapy TTD models

Distribution	AIC	BIC
Exponential	445.1522	447.8618
Weibull	418.3855	423.8045
Gamma	416.0335	421.4525
Gompertz	431.6542	437.0732
Lognormal	427.0343	432.4534
Loglogistic	418.9192	424.3382
Generalised-gamma	418.0262	426.1548
Spline models:		
1-spline hazard	418.1382	426.2668
1-spline odds	416.8364	424.9650
1-spline normal	416.6963	424.8249
2-spline hazard	418.2313	429.0694
2-spline odds	418.7268	429.5649
2-spline normal	418.0363	428.8744

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; TTD: time to discontinuation.

5.3.4.1 Selection of the base-case TTD parametric distribution

Visual inspection of the TTD distributions judged to be of sufficient statistical fit against the Kaplan-Meier trial data did not reveal any clear choices for a base case distribution. However, analysis of mean TTD under different curve choices highlighted that whilst the choice of distribution for the comparator arm had little effect on TTD, the choice of distribution for nivolumab had a considerable influence on mean TTD estimates. Table 35 presents the mean TTD for the different distributions.

Table 35: Summary of predicted mean TTD values for nivolumab and IC

Distribution	Predicted mean TTD - nivolumab	Predicted mean TTD - IC
2-spline odds	[redacted]	3.4
2-spline normal	[redacted]	3.3
Generalised-gamma	[redacted]	3.3
Loglogistic	[redacted]	3.6

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: IC: investigator's choice; TTD: time to discontinuation.

The long-term extrapolation of TTD with these four distributions is presented in Figure 38 for nivolumab and Figure 39 for IC.

Expert clinical opinion on treatment duration was clear that patients would not be expected to receive nivolumab indefinitely.[6] Due to the mechanism of action of the drug and patient preferences, patients could stop treatment if they had a good response (see Section 5.2.4). Specifically, based on feedback from a panel of eight international clinicians (including one UK clinician), treatment duration was expected not to exceed 1 year or at an absolute maximum 3 years.[6] The 2-spline odds and 2-spline normal model produced estimates of ~5% for the proportion of patients still on treatment at 4-years, which is inconsistent with expert clinical opinion. Furthermore, the long mean TTD with nivolumab predicted by these models (>10 months) was considered incompatible with the mean PFS of 4.6 months predicted by the base case PFS curve. Use of these curves for TTD and PFS, respectively, would imply that on average patients receive nivolumab for longer post-progression than pre-progression, which is clinically unrealistic and inconsistent with the fact that in the CheckMate 141 study 24.6% of patients continued treatment with nivolumab beyond progression.[14] Finally, these models estimate that the TTD curve is above the OS curve during the time horizon of the model (i.e. patients who have died are still receiving treatment with nivolumab), which is also clinically implausible.

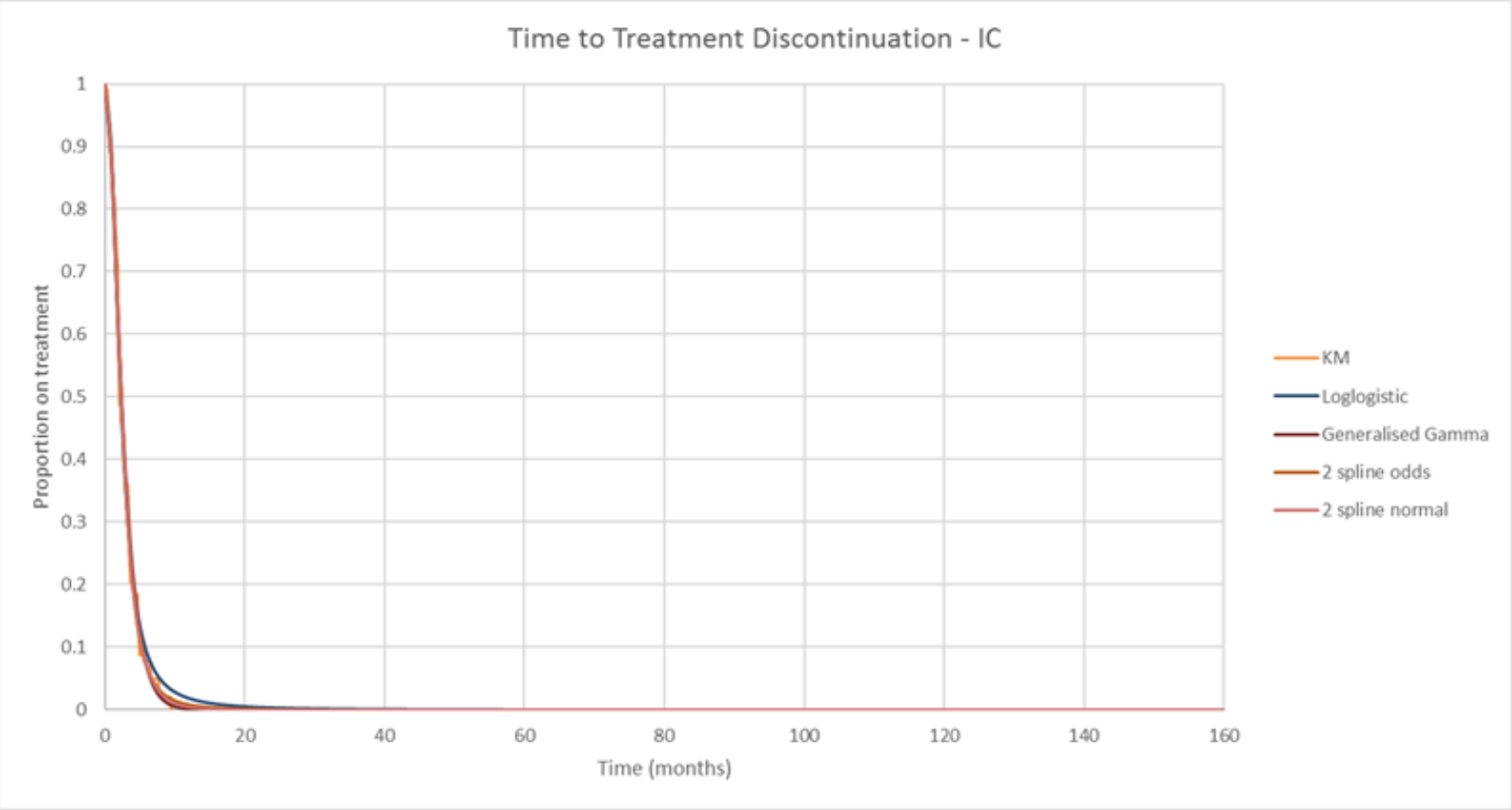
The loglogistic model was seen to have a slightly better statistical fit than the generalised gamma model for both nivolumab and IC and was therefore chosen as the base case distribution for TTD.

The impact of the choice of TTD curve was explored in scenario analyses that considered alternative distributions producing pessimistic and optimistic estimates for mean TTD with nivolumab (see Scenarios 8–9 in Section 5.8.3).

Figure 38: Long-term TTD extrapolation of best-fitting parametric models - nivolumab

Abbreviations: KM: Kaplan Meier; TTD: time to discontinuation.

Figure 39: Long-term TTD extrapolation of best-fitting parametric models - IC



Abbreviations: IC: investigator's choice; KM: Kaplan Meier; TTD: time to discontinuation.

5.3.5 Summary of survival analysis

The parametric survival models selected for the base case analysis are summarised in Table 36 alongside alternative survival functions that have been included in scenario analyses (see Scenarios 4–9 in Section 5.8.3).

Table 36: Summary of parametric survival models for OS, PFS and TTD

Choice of parametric curve in the base case analysis
OS
Nivolumab: lognormal **IC of therapy:** lognormal
PFS
Nivolumab: Generalised gamma **IC of therapy:** Generalised gamma
TTD
Nivolumab: Loglogistic **IC of therapy:** Loglogistic

Abbreviations: IC: investigator's choice; OS: overall survival; PFS: progression-free survival; TTD: time to discontinuation.

5.3.6 Adverse events

In the model, the costs and disutilities associated with AEs were estimated per episode (see Section 5.4.4 for disutilities and Section 5.5.5 for costs), and were applied once during the first cycle of the model based on the proportion of patients in each treatment arm experiencing each AE.

The initial inclusion criteria for AEs in the economic model were any all-cause Grade 3 or 4 AE with an incidence of ≥5% in either arm of the CheckMate 141 trial (see Table 37). These inclusion criteria have been used before in previous economic evaluations submitted to NICE for nivolumab.[19] Clinical experts were also consulted to validate these AEs and to confirm that no AEs with a meaningful cost or disutility had been omitted using these criteria.[7] Based on expert clinician feedback, dysphagia, nausea and vomiting, and anorexia were also recommended for inclusion in the model; these AEs are considered to be highly relevant to patients due to the anatomical location of head and neck tumours.[7]

Table 37: All-cause Grade 3 or 4 adverse events that were included in the model

Adverse event, n (%)	Incidence in CheckMate 141		Justification for inclusion
	Nivolumab (n=236)	IC (n=111)	
Fatigue	8 (3.4)	7 (6.3)	Incidence of ≥5% in either arm of CheckMate 141
Dyspnoea	13 (5.5)	2 (1.8)	
Hyponatraemia	11 (4.7)	9 (8.1)	
Anaemia	14 (5.9)	9 (8.1)	
Neutropenia	0	8 (7.2)	
Dysphagia	9 (3.8)	3 (2.7)	Identified by UK clinicians as being relevant to patients
Nausea and vomiting[a]	2 (0.8)	1 (0.9)	
Anorexia[b]	3 (1.3)	4 (3.6)	

[a] Sum of nausea and vomiting (reported separately). [b] Reported as decreased appetite.

Abbreviations: IC: investigator's choice.
Source: CheckMate 141 CSR (7th June 2016) – Table S.6.3[14]

5.4 Measurement and valuation of health effects

SCCHN has a highly detrimental impact on patient HRQoL, with patients experiencing significant impairments in functional, social and psychological well-being (as described in Section 3.1). For patients with platinum-refractory R/M SCCHN, the aim of treatment is largely palliative; however, currently-available therapies are often unable to improve or maintain levels of HRQoL (see Section 4.7.2). As reported in other cancer indications, disease progression is often associated with a reduction in health status compared to the progression-free state;[123] this post-progression decline in general health status was also observed in CheckMate 141 (see Section 5.4.1).[22]

5.4.1 Health-related quality-of-life data from clinical trials

As detailed in Section 4.3.3, HRQoL data were collected in the CheckMate 141 trial using the EQ-5D-3L questionnaire. Patients were scheduled to complete the EQ-5D-3L questionnaire during treatment visits at Week 1 (baseline) and then every 6 weeks from Week 9 onwards.[14] Follow-up for responses was also undertaken at Follow-Up visits 1 and 2[i] and during Survival Follow-Up visits.[14]

The EQ-5D descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, which are assessed in three levels: no problems, some problems, severe problems.[67] Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility representing the societal desirability of his/her own health. Patient-level EQ-5D responses from CheckMate 141 were converted to utility index-based scores using the UK-specific scoring algorithm published by Dolan *et al.* (1997).[72] The use of utility values in the model derived from patient-level EQ-5D data using a UK-specific tariff is consistent with recommendations provided in the NICE reference case.[25]

[i] Follow-Up Visit 1 was scheduled for 35 days from the last dose ±7 days or coincided with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose. Follow-Up Visit 2 was scheduled for 80 days (±7 days) from Follow-Up Visit 1. Survival follow-up visits were scheduled for every 3 months (± 7 days) from Follow-Up Visit 2.

Treatment-specific (i.e. nivolumab or IC of therapy) mean utilities were calculated for the PF and PD states (see Table 38). For each individual EQ-5D-3L assessment, the assessment date was compared to the date of RECIST-defined progression for that particular patient in order to specify the progression status into which the observation fell. Patients included in the analysis were all randomised patients who had any non-missing EQ-5D-3L and tumour response data; this corresponded to a total of [redacted] ([redacted]%) of patients in the nivolumab group and [redacted] ([redacted]%) of IC patients in the IC group.[22] As some of these patients contributed multiple observations, this corresponded to a total of [redacted] observations in the nivolumab group and [redacted] observations in the IC group.[22] The number of observations for each treatment arm by progression status is provided in Table 38. These values were applied to the corresponding model health states for each of the respective treatment cohorts. The use of overall utility values (based on all trial patients, regardless of treatment group) for both treatment cohorts was also explored in a scenario analyses (see Scenario 12 in Section 5.8.3).

Table 38: UK-specific health-state utilities derived from CheckMate 141 EQ-5D-3L data

Health state	Nivolumab		IC of therapy		Overall	
	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N = Number of observations, corresponding to the total number of EQ-5D-3L responses across all patients in that progression state who contributed at least one EQ-5D-3L response.

Abbreviations: CI: confidence intervals; EQ-5D-3L: 3-level EuroQoL-5 Dimensions; IC: investigator's choice.
Source: Bristol-Myers Squibb – Analysis of Quality-of-Life Endpoints in CheckMate 141. Data on File No.: OR NIVO 059.[22]

In a condition such as R/M SCCHN where patients face detrimental impacts to HRQoL, there is a risk that compliance rates for completion of questionnaires such as the EQ-5D-3L may suffer as the trial progresses and patients become too unwell to complete these assessments. Low response rates have the potential to mean that utility values can be based on a self-selected population of patients well enough to complete assessment and hence represent biased estimates. This was noted in the previous appraisal of nivolumab for the treatment of locally advanced or metastatic squamous NSCLC.[35]

Completion rates for the EQ-5D-3L questionnaire in CheckMate-141 are presented in Table 39. Similar to the other PROs assessed in CheckMate 141, fewer than 10 patients in the IC arm were eligible for on-treatment assessment using the EQ-5D-3L after Week 21.[124]

Table 39: EQ-5D-3L questionnaire completion rate summary from CheckMate 141

Time point	Nivolumab (n=240)		IC (n=121)	
	N[a]	n (%)[b]	N[a]	n (%)[b]
Baseline	240	191 (79.6)	121	90 (74.4)
Week 9	131	103 (78.6)	57	35 (61.4)
Week 15	85	58 (68.2)	30	16 (53.3)
Week 21	58	48 (82.8)	14	7 (50.0)
Week 27	44	31 (70.5)	5	2 (40.0)
Week 33	30	21 (70.0)	3	2 (66.7)
Week 39	19	9 (47.4)	1	1 (100)
Week 45	15	11 (73.3)	0 (0)	0 (0)
Week 51	9	6 (66.7)	0 (0)	0 (0)
Week 57	5	3 (60.0)	0 (0)	0 (0)
Week 63	2	0 (0)	0 (0)	0 (0)
Week 69	2	2 (100)	0 (0)	0 (0)
Follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]

[a] N = Number of subjects in study. [b] n = Number of questionnaires received; % = completion rate, where completion is defined as a non-missing response in at least 1 of EQ-5D dimensions: Mobility, Self Care, Activity, Pain, Anxiety and VAS.
Follow-Up Visit 1 was scheduled for 35 days from the last dose ±7 days or coincided with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose. Follow-Up Visit 2 was scheduled for 80 days (±7 days) from Follow-Up Visit 1.
Survival Follow-Up visits were scheduled for every 3 months after Follow-Up visit 2.

Abbreviations: EQ-5D-3L: 3-level EuroQoL-5 Dimensions; IC: investigator's choice; VAS: visual analogue scale.
Source: Bristol-Myers Squibb – Additional Analyses of Data Collected in CheckMate 141. Data on File No.: OR NIVO 058.[124]

In order to consider the possible risk of a selection bias in the completion of the EQ-5D-3L in CheckMate 141, a repeat of the above utility analysis was performed in which EQ-5D data from the first 21 weeks of the trial only was considered (see Table 40). This aimed to identify whether there was evidence of lower average PF utility scores with this earlier time-point cut-off. For this analysis there were a total of [redacted] respondents and [redacted] respondents included in the nivolumab group and IC group, respectively.[22] This corresponded to a total of [redacted] observations in the nivolumab group and [redacted] observations in the IC group in the PF state.[22]

Table 40: UK-specific *progression-free* state utilities derived from CheckMate 141 EQ-5D-3L data (up to Week 21)

Health state	Nivolumab		IC of therapy		Overall	
	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N = Number of observations, corresponding to the total number of EQ-5D-3L responses across all patients in that progression state who contributed at least one EQ-5D-3L response.

Abbreviations: CI: confidence intervals; EQ-5D: 3-level EuroQoL-5 Dimensions; IC: investigator's choice.
Source: Bristol-Myers Squibb – Analysis of Quality-of-Life Endpoints in CheckMate 141. Data on File No.: OR NIVO 059. [22]

A comparison of mean values in Table 38 and Table 40 shows that the utility values reported for patients in the PF state are similar for the analysis at the Week 21 cut-off as for the analysis over the whole trial period, for both the nivolumab and IC arms. The PF utility value for nivolumab is 0.049 higher than for IC in the analysis with all responses and 0.032 higher than IC for the analysis up to 21 weeks only. This difference in the incremental utility benefit for nivolumab over IC in the PF state between the two analyses is therefore only 0.017 (=0.049 – 0.032). If selection bias were a concern one would expect to see notably lower utility values for progression-free patients in the Week 21 analysis; this is not the case, suggesting that the utility values over all responses presented in Table 38 are reliable estimates.

5.4.2 Mapping

Mapping was not used within this economic evaluation.

5.4.3 Health-related quality-of-life studies

An SLR to identify relevant utility studies was performed, as described in Section 5.1, using the inclusion and exclusion criteria defined in Table 23. Only one study was identified that reported health-state utility values exclusively.[125] In this study, utilities were derived from members of the Canadian general public using the standard gamble approach for a variety of health states related to head and neck cancer (including recurrent or metastatic disease; see Appendix 10).[125]

In addition, one published economic evaluation identified in the SLR also reported health-state utilities.[113] The utilities included in this study were based on those used in the model submitted to NICE for the appraisal of cetuximab in combination with platinum-based therapy for R/M SCCHN [TA172, 2009].[23, 113] According to the manufacturer's submission, these utilities were derived from HRQoL data collected in the EXTREME trial using the EORTC QLQ-C30 questionnaire via the use of a mapping algorithm. Utility values used in the cost-effectiveness analysis submitted to NICE as part of TA172 are presented in Table 41.[23] These values are broadly similar to those observed in the IC arm of CheckMate 141 for PF and PD indicating a consistency with other measures of utility with standard chemotherapy treatment. However, such comparisons should be interpreted with caution as key differences exist in with regards to patient populations and study treatments (patients in the EXTREME trial were not refractory to platinum-based therapy and received either cetuximab plus platinum-based therapy or platinum-based therapy alone),[23] as well as the methods of eliciting utility values (mapping from the EORTC-QLQ-C30 versus directly collected EQ-5D data).[23]

Table 41: Utility values reported in the manufacturer's submission for TA172

Health state	Utility value
Stable/response with cetuximab	0.69
Stable/response with standard treatment	0.65
Progressive disease	0.52

Patients in the control arm of the EXTREME trial received platinum-based therapy alone (cisplatin or carboplatin plus fluorouracil). Cetuximab was given in combination with platinum-based therapy.

Source: NICE TA172 (2009) – Manufacturer's submission[23]

In the absence of any published, UK-specific utility data identified in the SLR that were elicited using methods preferred by NICE, utility data from the CheckMate 141 trial were considered to be most relevant to the decision problem for this appraisal. The utilities based on CheckMate 141 data were derived using UK-weighted EQ-5D-3L index values,[72] as preferred for the NICE reference case,[25] and were elicited from the exact population under consideration in this appraisal.

5.4.4 Adverse events

The economic model includes the disutilities for all-cause Grade 3 or 4 AEs which occurred in ≥5% of patients in either arm of CheckMate 141 (see Section 5.3.6). The disutility per episode associated with each AE is presented in Table 42. These utility decrements were applied separately for each AE and were applied once during the first cycle of the model (i.e. without discounting), based on the proportion of patients in each treatment arm experiencing each AE (as detailed in Section 5.3.6).

Due to a lack of published disutility values for AEs in SCCHN specifically, disutilities for AEs included in the model have instead been obtained from studies and previous technology appraisals reporting disutilities from patients with advanced lung cancer and gastrointestinal malignancies.[126, 127] The use of utility data from these indications was considered reasonable by a UK clinical expert given the similarities between these patient populations in terms of comorbidities and demographics (e.g. tobacco use and alcohol consumption).[7] No disutility value was available from these studies for the AE hyponatraemia and so a disutility of zero was assumed. As the incidence of hyponatraemia is higher in the IC arm than the nivolumab arm, this represents a conservative assumption. For anaemia, no disutility was reported and hence this disutility was assumed to be the same as that of fatigue based on expert clinical opinion.

The health state utility values presented in Section 5.4.1 were treatment-specific and therefore implicitly captured the utility impact of AEs experienced on therapy. As such, there is a risk that applying the disutilities for AEs in Table 42 may result in double-counting of the disutility associated with AEs experienced on treatment. A scenario analysis has therefore been included in which the disutility values for all AEs were set to zero (i.e. no specific AE disutility is modelled; see Scenario 13 in Section 5.8.3).

Table 42: Disutilities of adverse events included in the model

Adverse event	Disutility	Source
Fatigue	-0.07346	Nafees *et al.* (2008)[126]
Dyspnoea	-0.05	Doyle *et al.* (2008)[128]
Hyponatraemia	0	Assumption
Anaemia	-0.07346	Nafees *et al.* (2008)[126]
Neutropenia	-0.08973	Nafees *et al.* (2008)[126]
Dysphagia	-0.04802	Assumed to be the same as for nausea and vomiting
Nausea and vomiting	-0.04802	Nafees *et al.* (2008)[126]
Anorexia	-0.153	NICE TA378[127]

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

A summary of the utility values included in the base case analysis is presented in Table 43.

As described above, scenario analyses were also conducted in order to explore the impact of:

1. Assuming no differential health state utility between nivolumab and the modelled comparators by using health state utilities for the overall trial population in CheckMate 141 for all therapies in the model (see Scenario 12 in Section 5.8.3). Mean health state utilities (SD) [95% CI] from the overall trial population were [redacted] for PF and [redacted] for PD.[22]

2. Assuming no disutility arising from AEs as the treatment-specific health state utilities already included in the model may implicitly capture the utility impact of AEs experienced on therapy (see Scenario 13 in Section 5.8.3)

Table 43. Summary of utility values for cost-effectiveness analysis

Health State	Utility value: mean (SD)	95% CI	Reference in the submission	Justification
Nivolumab			Section 5.4.1	Derived from patient-level EQ-5D-3L data collected in CheckMate 141[22]*
Progression-free	[redacted]	[redacted]		
Progressed disease	[redacted]	[redacted]		
IC of therapy				
Progression-free	[redacted]	[redacted]		
Progressed disease	[redacted]	[redacted]		
Death	0	-		Assumption
All cause Grade 3 or 4 AE with ≥5% incidence	**Disutility value: mean**			
Fatigue	-0.07346	-	Section 5.3.6	Derived from published study in advanced lung cancer – lack of data for this AE in SCCHN, specifically
Dyspnoea	-0.05	-		Derived from published study in advanced lung cancer – lack of data for this AE in SCCHN, specifically
Hyponatraemia	0	-		Conservative assumption (lower incidence with nivolumab versus IC)
Anaemia	-0.07346	-		Assumed to be same as fatigue, as per previous appraisal
Neutropenia	-0.08973	-		Derived from published study in advanced lung cancer – lack of data for this AE in SCCHN, specifically
Dysphagia	-0.04802	-		Assumed to be the same as for nausea and vomiting
Nausea and vomiting	-0.04802	-		Derived from published study in advanced lung cancer – lack of data for this AE in SCCHN, specifically
Anorexia	-0.153	-		Based on previous appraisal

* Health-state utility data from the overall CheckMate 141 population were also used in a scenario analysis (Scenario 12), mean (SD) [95% CI]: PF = [redacted]; PD = [redacted].[22]

Abbreviations: AE: adverse event; CI: confidence intervals; CR: complete response; EQ-5D-3L: 3-level EuroQoL-5 Dimensions; NSCLC: non-small cell lung cancer; PD; progressed disease; PF: progression-free; SD: standard deviation.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

An SLR to identify relevant cost/resource use data was performed, as described in Section 5.1, using the inclusion and exclusion criteria defined in Table 23. A total of 38 studies were identified that reported cost/resource use data for the treatment of SCCHN (see Appendix 11). Of these, one UK study of treatment patterns and healthcare resource utilisation associated with repeatedly-treated metastatic SCCHN reported relevant data for inclusion in the cost-effectiveness analysis (see Appendix 11 for further details).[5]

In the absence of any additional sources of evidence, assumptions were made for cost/resource inputs included in the model where necessary and were validated through discussions with clinicians.[7]

5.5.2 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs for the intervention (nivolumab) and comparators (docetaxel, paclitaxel, and methotrexate) included in the model are presented in Table 44. Drug acquisition costs were obtained from the British National Formulary (BNF, 2016) for nivolumab and from the electronic market information tool (eMit, 2015) for generic comparator products.

As detailed in Section 2.3, a PAS has been agreed for nivolumab whereby a confidential discount is applied to the cost per vial (100 mg or 40 mg). Results of the cost-effectiveness analysis are presented with and without the PAS applied to the acquisition cost for nivolumab.

Dose frequency – weight, body surface area and dose delays

The dosing frequency of each technology used in the base case analysis of the model was based on the schedule followed in the CheckMate 141 trial:

- **Nivolumab:** 3 mg/kg, Q2W, intravenous (i.v.)
- **Docetaxel:** 30 mg/m^2, QW, i.v.
- **Methotrexate:** 40 mg/m^2, QW, i.v.

The dosage for nivolumab was calculated based on body weight in kilograms (kg) and the dosages for docetaxel, paclitaxel and methotrexate were calculated based on body surface area (BSA). Mean weight and BSA were based on the population of European patients in CheckMate 141 ([redacted] kg [SD, [redacted] and [redacted] m^2 [SD, [redacted]], respectively), based on an assumption that the European patients were more likely to reflect the weight and BSA characteristics of a UK population than the whole trial population.[124] Weight and BSA inputs based on UK patients included in CheckMate 141 were not used due to the small sample size (n=34); these were however similar to those reported from the larger European population.[124] Use of weight and BSA inputs for the whole trial population was explored in a scenario analysis (see Scenario 20 in Section 5.8.3). Similarly, a scenario analysis using BSA from a retrospective study of UK cancer patients, specifically, including head and neck patients, was also conducted (see Scenario 21 in Section 5.8.3).[129]

In order to account for the distribution in weight and BSA profiles amongst the population, both weight and BSA were modelled to be normally distributed. A normal distribution for BSA is supported by a retrospective study of average BSA in a population of UK cancer patients, including head and neck patients.[129] A normal distribution for weight was assumed based on no identification of evidence to the contrary and for alignment with the distribution applied for BSA given that weight and BSA are related measures. Mean and median weight in the trial were seen to be similar, further supporting a normal distribution and a normal distribution for weight has previously been accepted by NICE in appraisals that have included therapies with weight-based dosing.[130] These distributions were derived from the mean and SD values from CheckMate 141 given above and were used to estimate the proportion of patients requiring each possible number of vials, assuming no vial sharing occurs.

In the base case analysis, drug wastage (i.e. no vial sharing) was assumed for all therapies in order to be conservative about the expected cost of nivolumab. Costs per cycle were calculated assuming that pharmacists would use the optimum combination of vial sizes to reach the required dose, rounding up to the nearest full vial. In clinical practice, the use of nivolumab in other indications (specifically, melanoma, lung and renal cell carcinoma) may mean that hospital pharmacies can implement vial sharing across patients receiving nivolumab. The use of vial sharing was therefore included in a scenario analysis (see Scenario 15 in Section 5.8.3).

In CheckMate 141, dose delays were permitted for patients in both of the two treatment groups.[14] For consistency with the clinical data used in the model and to reflect expected clinical practice, a dose intensity reduction was calculated based on the proportion of doses received that were delayed in CheckMate 141.[14] Dose intensity was estimated to be [redacted]%, [redacted]% and [redacted]% for nivolumab, docetaxel and methotrexate, respectively. This calculation relied on the assumption that a dose delay was equivalent to a single missed dose for nivolumab (Q2W), methotrexate or docetaxel (QW for both) – in CheckMate 141, the average dose delay was [redacted] days for nivolumab, [redacted] days for methotrexate and [redacted] days for docetaxel.[124] The drug acquisition cost was therefore adjusted to account for the reduced dose intensity received by patients in CheckMate 141 due to dose delays, specifically – a similar approach has been taken for other appraisals of nivolumab to account for dose intensity.[120] As such, it was assumed that the drug would not be prepared for these dose delays and that a cost would therefore not be incurred by the NHS. To be conservative, administration costs were not however reduced, as it may the case that the chair time for an infusion had already been reserved and cannot be used by another patient. A scenario analysis in which no reductions in dose intensity were assumed (i.e. 100% dose intensity) was also explored (see Scenario 16 in Section 5.8.3).

The dosing frequency of docetaxel that is most routinely used in UK clinical practice is 75 mg/m^2, once every 3 weeks. Costs associated with this dosing frequency for docetaxel were applied to the model in a scenario analysis, with the same reductions in dose intensity modelled as for the QW regimen (see Scenario 14 in Section 5.8.3). The use of the 30 mg/m^2, QW, schedule in the base case analysis was chosen to ensure consistency with the trial regimen from which efficacy and safety inputs for the model were derived.

Paclitaxel, which was not included as a treatment option in the IC arm of CheckMate 141, was included in the model at a dosage of 80 mg/m^2 QW, based on the dose that is most frequently used by practicing clinicians in the UK.[7]

- **Paclitaxel:** 80 mg/m^2, QW, i.v.

The reduction in dose intensity calculated for docetaxel 30 mg/m^2, QW ([redacted]%) was also applied to paclitaxel QW, in the absence of data for paclitaxel 80 mg/m^2, QW, specifically.

Table 44: Drug acquisition costs – assuming wastage

Treatment	Dose required	Unit (vial)	Cost per vial	Cost per dose (weighted average)*	Doses per cycle	Cost per cycle
Nivolumab (without PAS)	3 mg/kg, Q2W	100 mg	£1,097.00	£[redacted]	2	£[redacted]
		40 mg	£439.00			
Nivolumab (with PAS)	3 mg/kg, Q2W	100 mg	£[redacted]	£[redacted]	2	£[redacted]
		40 mg	£[redacted]			
Docetaxel	30 mg/m^2, QW	80 mg	£12.47	£12.47	4	£49.88
Paclitaxel	80 mg/m^2, QW	100 mg	£8.50	£17.21	4	£68.84
Methotrexate	40 mg/m^2, QW	500 mg	£12.19	£12.19	4	£48.76

* Adjusted for patient distributions of weight (nivolumab) and BSA (docetaxel, paclitaxel and methotrexate).

Abbreviations: BNF: British National Formulary; BSA: body surface area; eMit: electronic market information tool; Q2W: once every two weeks; QW: once weekly.
Source: eMit 2015 for docetaxel, paclitaxel and methotrexate formulations and list price; BNF for nivolumab formulation and list price

Drug administration and monitoring costs

The costs of drug administration and monitoring for the intervention (nivolumab) and comparators (docetaxel, paclitaxel, and methotrexate) included in the model are presented in Table 45. Costs were derived from the NHS reference cost schedule 2014–15.[131]

There are no Healthcare Resource Group (HRG) or Payment by Results (PbR) codes specific to nivolumab; however, it is expected to be administered at a hospital outpatient setting and is assumed to be costed as a simple chemotherapy, as noted in previous appraisals for nivolumab.[19, 20] All therapies included in the model (all intravenously-administered) were therefore assumed to incur the same administration costs.

The type and frequency of monitoring visits were assumed to be the same for all patients included in the model who were receiving initial systemic therapy. For patients who had discontinued initial systemic therapy, monitoring costs were assumed to decrease to an oncologist visit with cell blood count, every 12 weeks (0.33 cycles).

Table 45: Drug administration and monitoring costs

Treatment	Setting	Cost code	Description	Unit cost	
Administration					
All therapies	Outpatient	SB12Z	Deliver simple parenteral chemotherapy at first attendance	£185.53	
Monitoring	**Frequency per cycle**	**Cost code**	**Description**	**Unit cost**	**Cost per cycle**
Monitoring – all patients prior to treatment discontinuation*					
Oncologist visit	1	WF01A	Non-admitted face-to-face attendance, follow-up for clinical oncologist (service code: 800)	£131.97	£131.97
Cell blood count	1	DAPS05	Directly assessed pathological services - haematology	£3.01	£3.01
CT scan	0.5	RD22Z	CT scan of one area, with pre and post contrast	£111.61	£55.81
Total monitoring costs per cycle					£190.79

* For patients who had discontinued initial systemic therapy, monitoring costs were assumed to decrease to an oncologist visit with single cell blood count, every 12 weeks (0.33 per cycle). Total cost per cycle = £44.99.

Abbreviations: CT: computerised tomography; NHS: National Health Service.
Source: NHS Reference Costs 2014–15[131]

5.5.3 Subsequent systemic therapy

In order to reflect what was observed in the trial, a proportion of patients who discontinued initial treatment in the model were assumed to receive subsequent systemic anti-cancer therapy, with costs accrued accordingly.[i] In the base case analysis, the proportion of patients who received subsequent systemic therapy post-discontinuation was based on clinical trial data from CheckMate 141 (see Table 46).

Table 46: Proportion of patients receiving subsequent systemic therapy in CheckMate 141

	Initial systemic therapy received in CheckMate 141	
	Nivolumab (n=240)	**IC of therapy (n=121)**
Patients who received subsequent systemic therapy, %	29.6%	32.2%

Source: CheckMate 141 CSR (7th June 2016) – Table 6.6-1[14]

Given the advanced stage of the disease, it was assumed that patients would only receive one additional systemic anti-cancer therapy post-discontinuation. Data on the duration of subsequent treatment was not available from the CheckMate 141 trial. It was therefore assumed that patients would receive subsequent therapy for 1.9 months; this reflected the median duration of therapy for patients in the IC arm of CheckMate 141, presented in Section 4.12, and was considered to be a reasonable assumption by clinical experts.[6]

Assumptions were also made regarding the choice of subsequent therapy based on what may be considered appropriate in current clinical practice. For example, patients who had received either

[i] As follow-up for OS in CheckMate 141 included the period following discontinuation of study treatment, the impact of subsequent therapies on survival is already accounted for in the model via the use of the extrapolated trial data

docetaxel or paclitaxel were assumed not to be treated with another taxane and were thus all assumed to receive methotrexate as a subsequent therapy (see Table 47). In CheckMate 141, a variety of subsequent therapies, including investigational therapies, were received by patients in addition to those listed below (see Appendix 3 for full details). For simplicity and applicability, the model restricts the choice of post-discontinuation therapies to those which would be expected to be used in current UK clinical practice (i.e. docetaxel and methotrexate). The dosing and cost of docetaxel and methotrexate were assumed to be the same as when used as an initial therapy (see Section 5.5.2).

Table 47: Distribution of modelled subsequent systemic therapies

	Subsequent systemic therapy	
Initial therapy	**Docetaxel**	**Methotrexate**
Nivolumab	50%	50%
Docetaxel	0%	100%
Paclitaxel	0%	100%
Methotrexate	100%	0%

Patients in the UK are not expected to receive either nivolumab or paclitaxel as subsequent systemic therapy. Only two patients in CheckMate 141 received subsequent systemic therapy with nivolumab,[14] and docetaxel is likely to be preferred over paclitaxel for those patients that would receive a taxane (see Section 3.2).

Additionally, scenario analyses were conducted in which:

1. The proportion of patients receiving subsequent therapy was reduced to 12% (see Scenario 17 in Section 5.8.3), based on market research on the proportion of patients expected to receive later-line therapy for R/M SCCHN[132]

2. The cost of subsequent systemic therapy was removed from the model (see Scenario 18 in Section 5.8.3)

5.5.4 Health-state unit costs and resource use

Progression-free disease and progressed disease

Patients incurred disease management costs for as long as they were alive in the model. Unit costs and the frequency of resource use per cycle were assumed to be constant between PF and PD health states, but the proportion of patients who received each resource use item varied depending on PF or PD. The type of resource and the proportion of patients who received each resource item were based on the UK study identified in the economic SLR (see Section 5.5.1), that reported treatment patterns and resource use in patients with repeatedly-treated metastatic SCCHN.[5] In the absence of specific data, it was assumed for simplicity that each resource item was used once per cycle. In addition, resource use items were only costed in the model if they were received by ≥10% of patients in either the PF or PD state (see Table 48).

Table 48: Disease-management costs by health state

Resource use item	Unit cost	Source	Frequency per cycle	Source	Progression-free		Progressed disease	
					% patients	Costs per cycle	% patients	Costs per cycle
Dental therapy for radiotherapy effects	£102.71	Total outpatient attendances (450) dental medicines specialties NHS reference cost 2014–15[131]	1	Nash-Smyth *et al.* (2015)[5]	22.3%	£22.91	9.8%	£10.07
Depression assessment and management	£73.20	Community Health Services, allied health professionals, A06A1: occupational therapist, adult, one-to-one NHS reference cost 2014–15[131]	1		12.8%	£9.37	11%	£8.05
Nutritional support	£79.47	Total other currencies, N16AF: specialist nursing, enteral feeding nursing services, adult, face-to-face NHS reference cost 2014–15[131]	1		58.6%	£46.57	49.4%	£39.26
Pain and symptom management / any supportive care	£78.67	Community Health Services, N21AF: specialist nursing, palliative/respite care, adult, face-to-face NHS reference cost 2014–15[131]	1		53.2%	£41.85	57.9%	£45.55
Speech and swallowing therapy	£86.58	Community Health Services, A13A1: speech and language therapist, adult, one-to-one NHS reference cost 2014–15[131]	1		22.3%	£19.31	9.2%	£7.97
Xerostomia management	£41.16	BNF 2016, pilocarpine (5-10 mg three times per day) as recommended in SIGN90[133]	1		24.1%	£9.92	14%	£5.76
Antiemetics	£0.44	eMIT 2015, assumed up to 8 mg per day for 5 days (ondansetron SPC)	1		59.6%	£0.26	39.6%	£0.17

Management of oral and gastrointestinal mucositis	£6.01	BNF 2016, 15 ml 4 times a day for 7 days (assuming one 300 ml bottle of benzydamine hydrochloride per cycle)	1		29.6%	£1.78	16.5%	£0.99
Hematologic growth factor/transfusions (1st unit) (first cycle only)	£170.14	NICE guideline [NG24] Blood Transfusion (2015)[134]	1		25.9%	£44.07	11.6%	£19.74
Hematologic growth factor/transfusions (subsequent units) (subsequent cycles)	£162.01	NICE guideline [NG24] Blood Transfusion (2015)[134]	1		25.9%	£41.96	11.6%	£18.79
Total costs per cycle: first cycle					**£196.03**		**£137.56**	
Total costs per cycle: subsequent cycles					**£193.93**		**£136.61**	

Abbreviations: BNF: British National Formulary; eMit: electronic market information tool; GP: general practitioner; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; SIGN: Scottish Intercollegiate Guidelines Network.

Additional health state costs: disease progression and terminal care

In addition to the health state costs accrued in PF and PD, the following one-off costs were also applied in the model:

- **Disease progression** – it was assumed that all patients who enter the PD state will have one oncologist visit and one CT scan in order to confirm disease progression
- **Terminal care** – it was assumed that patients who enter the death state would incur costs associated with terminal care. This was applied as a single cost which was based on the average cost of community and acute care for patients with cancer in the last eight weeks of their life from research conducted by the King's Fund (2008).[135] The same cost was applied in the model regardless of prior therapy received.[i]

The costs associated with each event are presented in Table 49.

Given the high unit cost associated with terminal care, a scenario analysis was conducted in which this one-off cost was removed from the model (see Scenario 19 in Section 5.8.3).

Table 49: One-off health state costs associated with disease progression and terminal care

Event	Resource use per event	Unit cost	Total cost	Source
Disease progression			£243.53	NHS reference cost 2014–15:[131] WF01A RD22Z
Oncologist visit	1 on entering PD	£131.97		
CT scan	1 on entering PD	£111.61		
Terminal care	1 on entering 'death'	£6,159.66	£6,159.66	NICE ID853[120] and Addicot and Dewar (2008)[135]

Abbreviations: CT: computerised tomography; NHS: National Health Service.

5.5.5 Adverse reaction unit costs and resource use

All-cause Grade 3 or 4 AEs that occurred in ≥5% of patients in either arm of CheckMate 141, and those that were considered clinically relevant by expert clinical opinion, were included in the model (see Section 5.3.6). The costs of treating AEs are per episode and were sourced using currency codes for NHS reference costs and assumptions used in previous appraisals.[19, 136]

[i] Not all of the costs included the calculation are direct NHS costs – some fall on 'third sector' healthcare organisations; however, their inclusion is relevant to the disease, and does not introduce any bias, as over 99% of patients died within the model time horizon in the base case analysis.

Table 50: Cost of adverse events

Adverse event	Cost per episode	Source
Fatigue	£3,110.11	Assumed to be the same as anaemia based on NICE TA347[136]
Dyspnoea	£0	NICE ID811[19] – based on previous appraisal of nivolumab
Hyponatraemia	£657.84	NICE ID811[19] – based on previous appraisal of nivolumab
Anaemia	£3,110.11	NICE TA347[136] Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 0-8+ (weighted average)[131]
Neutropenia	£478.31	NICE TA347[136] Agranulocytosis with CC Score 0-13+ (weighted average)[131]
Dysphagia	£3,305.54	NICE TA172[23] – inflated to 2014/15
Nausea and vomiting	£1,324.62	NICE TA172[23] – inflated to 2014/15
Anorexia	£402.57	NICE TA378[127] – inflated to 2014/15

5.5.6 Miscellaneous unit costs and resource use

No additional costs or resource use items were included in the model that have not already been listed above.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case *de novo* analysis inputs

A complete list of inputs used in the base case analysis, including measurements of uncertainty and distributions, are detailed in Appendix 12. A summary of the key variables is presented in Table 51.

Table 51: Summary of variables applied in the base case analysis

Area	Variable	Value	Reference in submission
General	Patient population	Adults with R/M SCCHN who have received platinum-based therapy	Section 5.2.1
	Time horizon	20 years (lifetime equivalent)	Section 5.2.2
	Model cycle length	4 weeks	
	Discount rate (costs and QALYs)	3.5%	
	Mean body weight (SD)	[redacted] kg ([redacted])	Section 5.5.2
	Mean BSA (SD)	[redacted] m^2 ([redacted])	
Efficacy	Survival function for OS	Nivolumab: lognormal Docetaxel/methotrexate/paclitaxel (all modelled with IC data): lognormal	Section 5.3.5
	Survival function for PFS	Nivolumab: generalised gamma Docetaxel/methotrexate/paclitaxel (all modelled with IC data): generalised gamma	
	Survival function for TTD	Nivolumab: loglogistic Docetaxel/methotrexate/paclitaxel (all modelled with IC data): loglogistic	
Subsequent treatment	Patients receiving subsequent therapy:		Section 5.5.3
	Nivolumab	29.6%	
	Comparators	32.2%	
	Number of subsequent therapies	1	
	Duration of subsequent therapy	1.9 months	
	Distribution of subsequent systemic therapy received, following initial therapy with:		
	Nivolumab	Docetaxel: 50% Methotrexate: 50%	

	Docetaxel	Methotrexate: 100%	
	Paclitaxel	Methotrexate: 100%	
	Methotrexate	Docetaxel: 100%	
Costs	Drug acquisition cost per 4-week cycle:		Section 5.5.2
	Nivolumab (without PAS)	£[redacted]	
	Nivolumab (with PAS)	£[redacted]	
	Docetaxel	£49.88	
	Paclitaxel	£68.84	
	Methotrexate	£48.76	
	Administration cost per dose (all therapies)	£183.53	
	Monitoring costs per cycle (all therapies – prior to treatment discontinuation)	£190.79	
	Monitoring costs per cycle (post-treatment discontinuation)	£44.99	
	PF cost per cycle		Section 5.5.4
	Cycle 1	£196.03	
	Subsequent cycles	£193.93	
	PD cost per cycle		
	Cycle 1	£137.56	
	Subsequent cycles	£136.61	
	Disease progression cost (per event)	£243.53	
	Terminal care cost (per event)	£6,159.66	
Adverse events	Incidence of adverse events with nivolumab	Fatigue: 3.4% Dyspnoea: 5.5% Hyponatraemia: 4.7% Anaemia: 5.9% Neutropenia: 0% Dysphagia: 3.8% Nausea and vomiting: 0.8% Anorexia: 1.3%	Section 5.3.6
	Incidence of adverse events with comparators	Fatigue: 6.3% Dyspnoea: 1.8% Hyponatraemia: 8.1% Anaemia: 8.1% Neutropenia: 7.2% Dysphagia: 2.7% Nausea and vomiting: 0.9% Anorexia: 3.6%	
	Cost of fatigue (per episode)	£3,110.11	Section 5.5.5
	Cost of dyspnoea (per episode)	£0	

	Cost of hyponatraemia (per episode)	£657.84		
	Cost of anaemia (per episode)	£3,110.11		
	Cost of neutropenia (per episode)	£478.31		
	Cost of dysphagia (per episode)	£3,305.54		
	Cost of nausea and vomiting (per episode)	£1,324.62		
	Cost of anorexia (per episode)	£402.57		
Utility	Health state, by treatment Mean (SD)	Nivolumab	Comparators	Section 5.4.1
	PF	[redacted]	[redacted]	
	PD	[redacted]	[redacted]	
	Death	0	0	
Disutility of adverse events	Fatigue	-0.07346		Section 5.4.4
	Dyspnoea	-0.05		
	Hyponatraemia	0		
	Anaemia	-0.07346		
	Neutropenia	-0.08973		
	Dysphagia	-0.04802		
	Nausea and vomiting	-0.04802		
	Anorexia	-0.153		

Abbreviations: BSA: body surface area; OS: overall survival; PD: progressive disease; PF: progression-free; PFS: progression-free survival; IC: investigator's choice; QALY: quality-adjusted life year; R/M: recurrent and/or metastatic; SCCHN: squamous-cell carcinoma of the head and neck; SD: standard deviation; TTD: time to discontinuation.

5.6.2 Assumptions

A list of the assumptions used in the base case analysis is provided in Table 52 alongside a list of scenarios conducted to explore the impact of these assumptions on the cost-effectiveness results. The results of these scenario analyses are presented in Section 5.8.3.

Table 52: List of assumptions for the base case analysis

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analyses
Treatment beyond progression	Costs associated with treatment were based on TTD rather than PFS	Treatment beyond RECIST-defined progression was permitted in the nivolumab arm of CheckMate 141 and is permitted in the SmPC. The use of TTD rather than PFS therefore provides a more accurate measure of treatment duration.	A scenario analysis using PFS to estimate treatment costs was also explored: **Scenario 10** In addition, alternative clinical stopping rules were also explored whereby treatment was stopped at 1, 2 and 3 years (see Section 5.8.3): **Scenarios 1–3**
Parametric survival distributions	Efficacy data to inform the model were extrapolated from CheckMate 141 using the following parametric survival models: OS: lognormal PFS: generalised gamma TTD: loglogistic	Extrapolation was required as trial follow-up did not match the model time horizon. The choice of parametric model was based on statistical goodness-of-fit, clinical plausibility and validation versus available sources of survival data.	Alternative survival functions for OS, PFS and TTD were also explored: **Scenarios 4–9**
Time horizon	20 years	In the model, >99% of all patients had died. A lifetime time horizon is consistent with the NICE reference case.	Additional time horizons (10, 15, and 25 years) were explored: **Scenario 11a–c**
Health-state utilities	Nivolumab and comparator therapies were assumed to be associated with different health-state utilities	Based on EQ-5D-3L data collected during CheckMate 141	A scenario analysis was conducted in which health-state utilities for all therapies were based on data from the overall trial population of CheckMate 141: **Scenario 12**
Disutility of adverse events	Disutilities for adverse events were derived from studies that included patients with advanced lung cancer	There is a lack of disutility data for relevant adverse events in the setting of SCCHN, specifically	A scenario analysis was conducted in which the disutility of adverse events was not included: **Scenario 13**
Treatment dosing and related	Dosing was based on that used in CheckMate 141 and included	Clinical data included in the model is based on results from the CheckMate 141 trial.	Scenario analyses were conducted in which:

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analyses
patient characteristics	reductions in dose intensity (based on dose delays in CheckMate 141). No vial sharing was assumed and weight and BSA inputs were based on European patients included in CheckMate 141	Drug wastage was assumed for all therapies in order to be conservative about the expected cost of nivolumab European weights and BSA inputs were assumed to be more representative of UK patients	The more routinely-used dose in the UK of 75 mg/m^2 Q3W for docetaxel was modelled: **Scenario 14** Vial sharing was permitted: **Scenario 15** Dose intensity was assumed to be 100% for all therapies: **Scenario 16** Weight and BSA were based on the whole trial population: **Scenario 20** BSA was based data from UK cancer patients,[129] including head and neck patients: **Scenario 21**
Subsequent systemic therapies	Patients received only one subsequent systemic therapy	Given the advanced nature of the disease, patients are not expected to receive more than one subsequent systemic therapy post-discontinuation	Scenario analyses were conducted in which: The proportion of patients receiving subsequent systemic therapy was reduced to 12%, based on market research: **Scenario 17** The cost of subsequent therapy was removed altogether: **Scenario 18**
Terminal care	Patients who entered the death state accrued a cost for terminal care	Given the limited life-expectancy of patients with R/M SCCHN, the majority of patients are expected to die as a result of their cancer	Terminal care costs were excluded as part of a scenario analysis: **Scenario 19**
Source of efficacy data	Clinical data from the IC arm of CheckMate 141 were applied to docetaxel, paclitaxel and methotrexate	Although the IC arm comprised multiple treatments of docetaxel, methotrexate or cetuximab, data from the IC arm was applied to all comparator therapies in the model in order to preserve sample size and trial randomisation. As a taxane, the efficacy of paclitaxel is expected to be similar to that of docetaxel (another taxane).	No alternative sources of relevant data were identified in the clinical SLR that could be used in scenario analyses

Abbreviations: BSA: body surface area; IC: investigator's choice; EQ-5D-3L: 3-level EuroQol 5-Dimensions; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; Q3W: once every three weeks; RECIST: Response Evaluation Criteria In Solid Tumours; R/M: resistant and/or metastatic; SCCHN: squamous-cell carcinoma of the head and neck; SmPC: Summary of Product Characteristics; TTD: time to discontinuation; UK: United Kingdom.

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

The deterministic base case results are presented in Table 53 for nivolumab (without PAS) versus each of docetaxel, paclitaxel and methotrexate and in Table 54, with the confidential PAS discount applied to nivolumab.

As the same clinical and utility data were applied to each comparator, the incremental QALYs gained with nivolumab versus each of docetaxel, paclitaxel and methotrexate were the same ([redacted], see Table 53 and Table 54). Nivolumab was associated with greater lifetime costs than each of the comparators, irrespective of whether the PAS for nivolumab was applied. The incremental cost associated with nivolumab (without PAS) versus comparators lay within a narrow range across the three comparators ([redacted]) and was reduced to [redacted] when the PAS for nivolumab was applied.

In the base case analysis, treatment with nivolumab (without PAS) was associated with an incremental cost per QALY of [redacted], [redacted] and [redacted] versus docetaxel, paclitaxel and methotrexate, respectively. With the PAS for nivolumab included, the incremental cost per QALY for nivolumab was reduced to £34,902, £34,777, and £34,908 versus docetaxel, paclitaxel and methotrexate, respectively. Under the end-of-life criteria that should be considered relevant to nivolumab in this appraisal (see Section 4.13.2), these base case ICERs fall below the cost-effectiveness threshold adopted by NICE of £50,000 per QALY.

Table 53: Deterministic base case results (without PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 54. Deterministic base case results (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

5.7.2 Clinical outcomes from the model

A comparison of clinical outcomes (PFS, TTD and OS) predicted by the base case analysis and CheckMate 141 is presented in Table 55. Compared to median OS, PFS and TTD from CheckMate 141, the model over-predicted median PFS and median TTD and under-predicted median OS for nivolumab (versus the nivolumab trial arm), whereas for the comparators, the

model provided very close estimates for median PFS and median OS and slightly over-predicted median TTD (versus the IC trial arm).

Table 55: Model predictors of clinical outcomes compared with CheckMate 141

Outcome, months (95% CI)	Nivolumab		Comparators*	
	CheckMate 141	Economic model	CheckMate 141	Economic model
PFS				
Median	2.0 (1.9, 2.1)	2.6	2.3 (1.9, 3.1)	2.6
Mean	-	4.6	-	3.6
TTD				
Median	1.9 (1.6, 2.3)	3.0	1.9 (1.6, 2.0)	2.30
Mean	-	[redacted]	-	3.6
OS				
Median	7.5 (5.5, 9.1)	7.1	5.1 (4.0, 6.0)	5.0
Mean	-	17.7	-	8.4

* Based on the total IC arm of CheckMate 141

Abbreviations: CI: confidence intervals; IC: investigator's choice; OS: overall survival; PFS: progression-free survival; TTD: time to discontinuation.
Source: Gillison *et al.* (2016),[8] and CheckMate 141 CSR (7th June 2016)[14] for OS and TTD; Ferris *et al.* (2016)[9] and CheckMate 141 CSR (7th June 2016)[14] for PFS

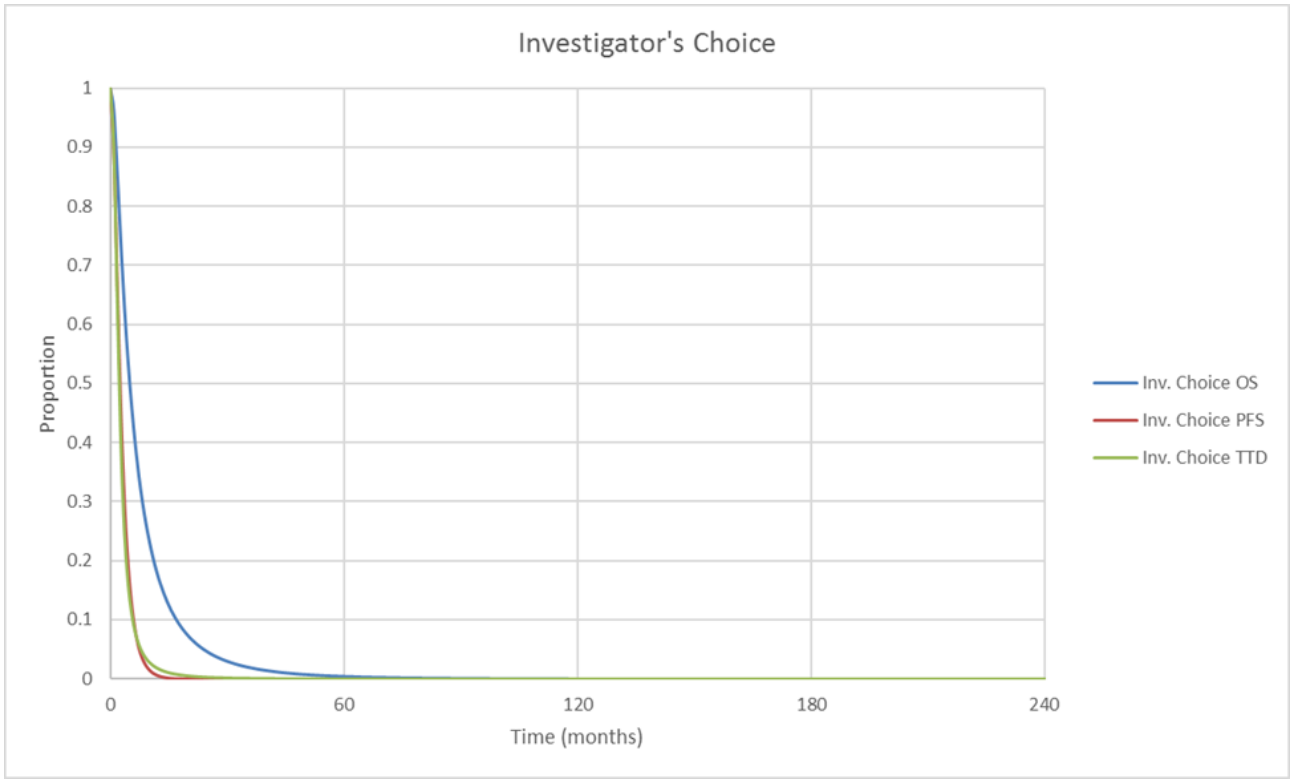
In the base-case analysis, all patients in each of the comparator cohorts had died by the end of the 20-year time horizon. The vast majority of patients in the nivolumab cohort had also died (>99%). The 20-year time horizon can therefore be considered to represent the entire lifetime of patients included in the model and is consistent with what is reasonably assumed to be the maximum life-expectancy of patients in clinical practice.

The distribution of patients between health states (PF and PD) in the base case analysis is presented for nivolumab and comparator therapies in Figure 40 and Figure 41, respectively. The extrapolated TTD curve is also presented on these cohort traces in order to show the proportion of patients still on initial therapy throughout the lifetime of the model. Reassuringly, the curves for TTD and PFS remain below the curve for the OS throughout the lifetime of the model in both cases highlighting that the combination of the parametric distributions chosen for OS, PFS and TTD is clinically plausible.

Figure 40: Cohort trace for nivolumab beyond 20 years (base case analysis)

Abbreviations: OS: overall survival; PFS: progression-free survival; TTD: time to discontinuation

Figure 41: Cohort trace for investigator's choice beyond 20 years (base case analysis)



Abbreviations: OS: overall survival; PFS: progression-free survival; TTD: time to discontinuation

5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

As the occupancy of each health state and the incidence of AEs was based on data from the IC arm of the CheckMate 141 trial applied to each model comparator, the disaggregated QALYs by health state (and those related to AEs) were the same for each comparison of nivolumab versus either docetaxel, paclitaxel or methotrexate.

The predicted QALYs by health state (and disutilities associated with AEs) for nivolumab and comparator therapies are presented in Table 56. The main source of benefit from treatment with nivolumab came from an extension in the period of time spent in the PD state. This substantial QALY gain in the PD state with nivolumab is reflective of the improved OS benefit of nivolumab versus comparators (see Section 5.7.2), and also the higher utility associated with nivolumab in the PD state (see Section 5.4.1). This latter point may relate to the fact that the PD utility value for nivolumab included any continuing health benefits for patients treated with nivolumab beyond disease progression, as this was only permitted in the CheckMate 141 trial if patients were perceived to be gaining continued benefit from treatment (see Section 5.2.4). A QALY gain for nivolumab versus comparators in the PF state was also predicted but this contributed much less to the overall QALY gain than those accrued in the PD state. This most likely reflects the similar PFS observed between the nivolumab and comparator cohorts (see Section 5.7.2). As noted in Section 4.7.2, a delayed separation of survival curves has been observed previously in other trials of nivolumab versus standard cytotoxic therapies.[19, 20] This is considered indicative of the limitations of using RECIST with immune-checkpoint inhibitors as a method of evaluating clinical benefit in terms of response or progression (see Section 4.3.3), as some patients may progress by RECIST criteria before exhibiting a clinical response.[19, 20] The impact of disutilities due to AEs on the incremental QALY gain was minimal with similarly small decrements in utility predicted with all therapies.

Table 56: Summary of QALY gain by health state – nivolumab versus comparators*

Health state	QALY intervention (nivolumab)	QALY comparator (IC)	Incremental QALYs	Absolute increment	% absolute increment
PF	[redacted]	0.18	[redacted]	[redacted]	15%
PD	[redacted]	0.22	[redacted]	[redacted]	83%
AE disutility	[redacted]	-0.03	[redacted]	[redacted]	2%
Total	[redacted]	0.37	[redacted]	[redacted]	100%

* Occupancy of health states and the incidence of AEs were based on the IC arm of CheckMate 141 for all comparators.

Abbreviations: AE: adverse event; IC: investigator's choice; PD: progressive disease; PF: progression-free; QALY: quality-adjusted life year.

Costs disaggregated by resource use category are presented in Table 57, Table 58 and Table 59 for nivolumab (without PAS) versus docetaxel, paclitaxel and methotrexate, respectively, and in Table 60, Table 61 and Table 62 with the PAS applied for nivolumab. Only the costs associated with drug acquisition and subsequent therapy for the comparators differed in each comparison (marked as bold in each table) – the percentage absolute increment for these resource items did not however vary considerably between these comparisons.

The overall differences in cost between each comparator and nivolumab were largely (~90%) due to the higher drug acquisition cost with nivolumab versus each comparator therapy.

Table 57: Summary of predicted resource use by category of cost – nivolumab versus docetaxel (without PAS for nivolumab)

Item	Cost intervention (nivolumab)	Cost comparator (docetaxel)	Incremental costs	Absolute increment	% absolute increment
PF disease management	[redacted]	£655	[redacted]	[redacted]	1%
PD disease management*	[redacted]	£6,805	[redacted]	[redacted]	3%
Disease progression (one-off cost)	[redacted]	£239	[redacted]	[redacted]	0%
Drug acquisition	[redacted]	**£170**	[redacted]	[redacted]	**91%**
Drug administration	[redacted]	£2,522	[redacted]	[redacted]	2%
Monitoring	[redacted]	£876	[redacted]	[redacted]	2%
Subsequent treatment	[redacted]	**£621**	[redacted]	[redacted]	**0%**
Adverse events	[redacted]	£651	[redacted]	[redacted]	1%
Total	[redacted]	£12,538	[redacted]	[redacted]	100%

Table 58: Summary of predicted resource use by category of cost – nivolumab versus paclitaxel (without PAS for nivolumab)

Item	Cost intervention (nivolumab)	Cost comparator (paclitaxel)	Incremental costs	Absolute increment	% absolute increment
PF disease management	[redacted]	£655	[redacted]	[redacted]	1%
PD disease management*	[redacted]	£6,805	[redacted]	[redacted]	3%
Disease progression (one-off cost)	[redacted]	£239	[redacted]	[redacted]	0%
Drug acquisition	[redacted]	**£234**	[redacted]	[redacted]	**91%**
Drug administration	[redacted]	£2,522	[redacted]	[redacted]	2%
Monitoring	[redacted]	£876	[redacted]	[redacted]	2%
Subsequent treatment	[redacted]	**£621**	[redacted]	[redacted]	**0%**
Adverse events	[redacted]	£651	[redacted]	[redacted]	1%
Total	[redacted]	£12,603	[redacted]	[redacted]	100%

Table 59: Summary of predicted resource use by category of cost – nivolumab versus methotrexate (without PAS for nivolumab)

Item	Cost intervention (nivolumab)	Cost comparator (methotrexate)	Incremental costs	Absolute increment	% absolute increment
PF disease management	[redacted]	£655	[redacted]	[redacted]	1%
PD disease management*	[redacted]	£6,805	[redacted]	[redacted]	3%
Disease progression (one-off cost)	[redacted]	£239	[redacted]	[redacted]	0%
Drug acquisition	[redacted]	**£166**	[redacted]	[redacted]	**91%**
Drug administration	[redacted]	£2,522	[redacted]	[redacted]	2%
Monitoring	[redacted]	£876	[redacted]	[redacted]	2%
Subsequent treatment	[redacted]	**£621**	[redacted]	[redacted]	**0%**
Adverse events	[redacted]	£651	[redacted]	[redacted]	1%
Total	[redacted]	£12,535	[redacted]	[redacted]	100%

Table 60: Summary of predicted resource use by category of cost – nivolumab versus docetaxel (with PAS for nivolumab)

Item	Cost intervention (nivolumab)	Cost comparator (docetaxel)	Incremental costs	Absolute increment	% absolute increment
PF disease management	[redacted]	£655	[redacted]	[redacted]	1%
PD disease management*	[redacted]	£6,805	[redacted]	[redacted]	5%
Disease progression (one-off cost)	[redacted]	£239	[redacted]	[redacted]	0%
Drug acquisition	[redacted]	**£170**	[redacted]	[redacted]	**87%**
Drug administration	[redacted]	£2,522	[redacted]	[redacted]	3%
Monitoring	[redacted]	£876	[redacted]	[redacted]	3%
Subsequent treatment	[redacted]	**£621**	[redacted]	[redacted]	**0%**
Adverse events	[redacted]	£651	[redacted]	[redacted]	1%
Total	[redacted]	£12,538	[redacted]	[redacted]	100%

Table 61: Summary of predicted resource use by category of cost – nivolumab versus paclitaxel (with PAS for nivolumab)

Item	Cost intervention (nivolumab)	Cost comparator (paclitaxel)	Incremental costs	Absolute increment	% absolute increment
PF disease management	[redacted]	£655	[redacted]	[redacted]	1%
PD disease management*	[redacted]	£6,805	[redacted]	[redacted]	5%
Disease progression (one-off cost)	[redacted]	£239	[redacted]	[redacted]	0%
Drug acquisition	[redacted]	**£234**	[redacted]	[redacted]	**87%**
Drug administration	[redacted]	£2,522	[redacted]	[redacted]	3%
Monitoring	[redacted]	£876	[redacted]	[redacted]	4%
Subsequent treatment	[redacted]	**£621**	[redacted]	[redacted]	**0%**
Adverse events	[redacted]	£651	[redacted]	[redacted]	1%
Total	[redacted]	£12,603	[redacted]	[redacted]	100%

Table 62: Summary of predicted resource use by category of cost – nivolumab versus methotrexate (with PAS for nivolumab)

Item	Cost intervention (nivolumab)	Cost comparator (methotrexate)	Incremental costs	Absolute increment	% absolute increment
PF disease management	[redacted]	£655	[redacted]	[redacted]	1%
PD disease management*	[redacted]	£6,805	[redacted]	[redacted]	5%
Disease progression (one-off cost)	[redacted]	£239	[redacted]	[redacted]	0%
Drug acquisition	[redacted]	**£166**	[redacted]	[redacted]	**87%**
Drug administration	[redacted]	£2,522	[redacted]	[redacted]	3%
Monitoring	[redacted]	£876	[redacted]	[redacted]	3%
Subsequent treatment	[redacted]	**£621**	[redacted]	[redacted]	**0%**
Adverse events	[redacted]	£651	[redacted]	[redacted]	1%
Total	[redacted]	£12,535	[redacted]	[redacted]	100%

For all tables:
* The one-off cost of terminal care was included in PD disease management costs.
Costs that change between comparators are given in bold.

Abbreviations: PD: progressed disease; PF: progression free; PAS: Patient Access Scheme.

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

The incremental results from the probabilistic sensitivity analyses (1,000 simulations; distributions used to perform the analysis are presented in Appendix 12) are presented in Table 63 for nivolumab (without PAS) versus each of docetaxel, paclitaxel and methotrexate, and in Table 64 with the confidential PAS discount applied to nivolumab. These results demonstrate that the probabilistic results (that take into account the combined uncertainty across model parameters) are similar to those estimated in the deterministic base case analysis.

Scatter plots of incremental costs and QALYs for nivolumab (without PAS) versus docetaxel, paclitaxel and methotrexate are presented in Figure 42, Figure 43 and Figure 44, respectively; and in Figure 45, Figure 46 and Figure 47 with the PAS applied for nivolumab.

Table 63: Probabilistic results (without PAS for nivolumab)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)
Nivolumab	[redacted]	[redacted]			
Docetaxel	12,547	0.37	[redacted]	[redacted]	[redacted]
Paclitaxel	12,621	0.37	[redacted]	[redacted]	[redacted]
Methotrexate	12,551	0.37	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 64: Probabilistic results (with PAS for nivolumab)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)
Nivolumab	[redacted]	[redacted]			
Docetaxel	£12,544	0.37	[redacted]	[redacted]	£35,157
Paclitaxel	£12,613	0.37	[redacted]	[redacted]	£35,025
Methotrexate	£12,576	0.37	[redacted]	[redacted]	£35,091

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Figure 42: Cost-effectiveness plane: nivolumab (without PAS) versus docetaxel – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 43: Cost-effectiveness plane: nivolumab (without PAS) versus paclitaxel – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 44: Cost-effectiveness plane: nivolumab (without PAS) versus methotrexate – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 45: Cost-effectiveness plane: nivolumab (with PAS) versus docetaxel – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 46: Cost-effectiveness plane: nivolumab (with PAS) versus paclitaxel – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 47: Cost-effectiveness plane: nivolumab (with PAS) versus methotrexate – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Cost-effectiveness acceptability curves for nivolumab (without PAS) versus docetaxel, paclitaxel and methotrexate are presented in Figure 48, Figure 49 and Figure 50, respectively; and in Figure 51, Figure 52 and Figure 53 with the PAS applied for nivolumab. When considering nivolumab to be provided with the PAS and at a cost-effectiveness threshold of £50,000 per QALY (the threshold considered by NICE for end of life medicines), nivolumab is associated with a probability of cost-effectiveness of greater than 70% against all comparators.

Figure 48: Cost-effectiveness acceptability curve: nivolumab (without PAS) versus docetaxel

Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

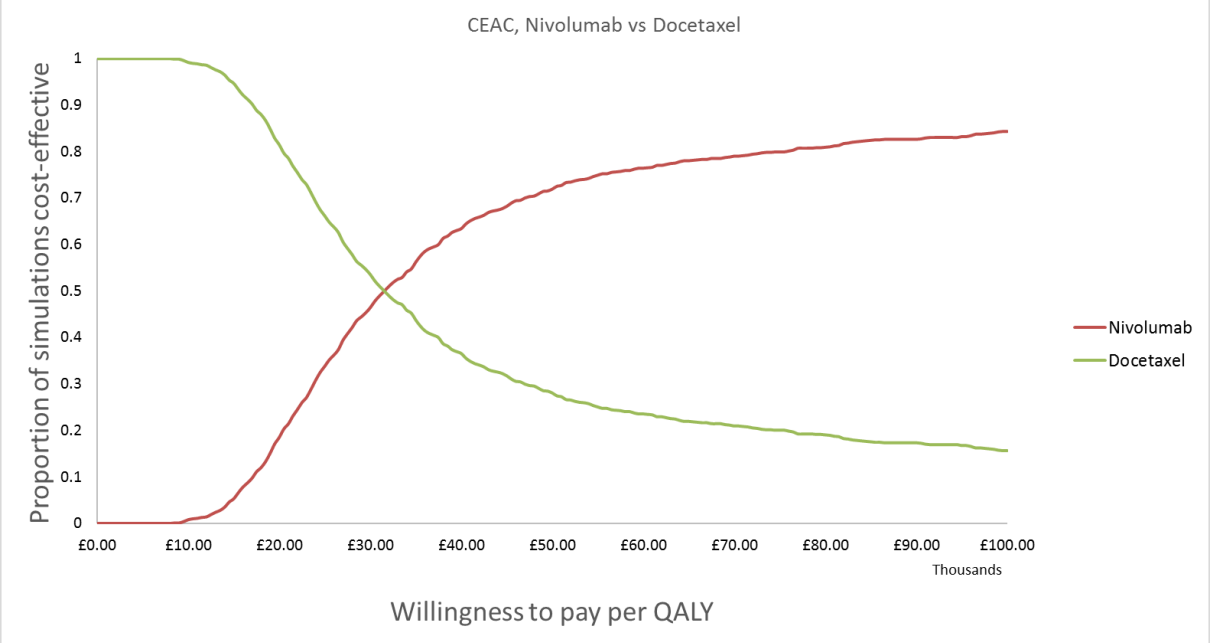
Figure 49: Cost-effectiveness acceptability curve: nivolumab (without PAS) versus paclitaxel

Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Figure 50: Cost-effectiveness acceptability curve: nivolumab (without PAS) versus methotrexate

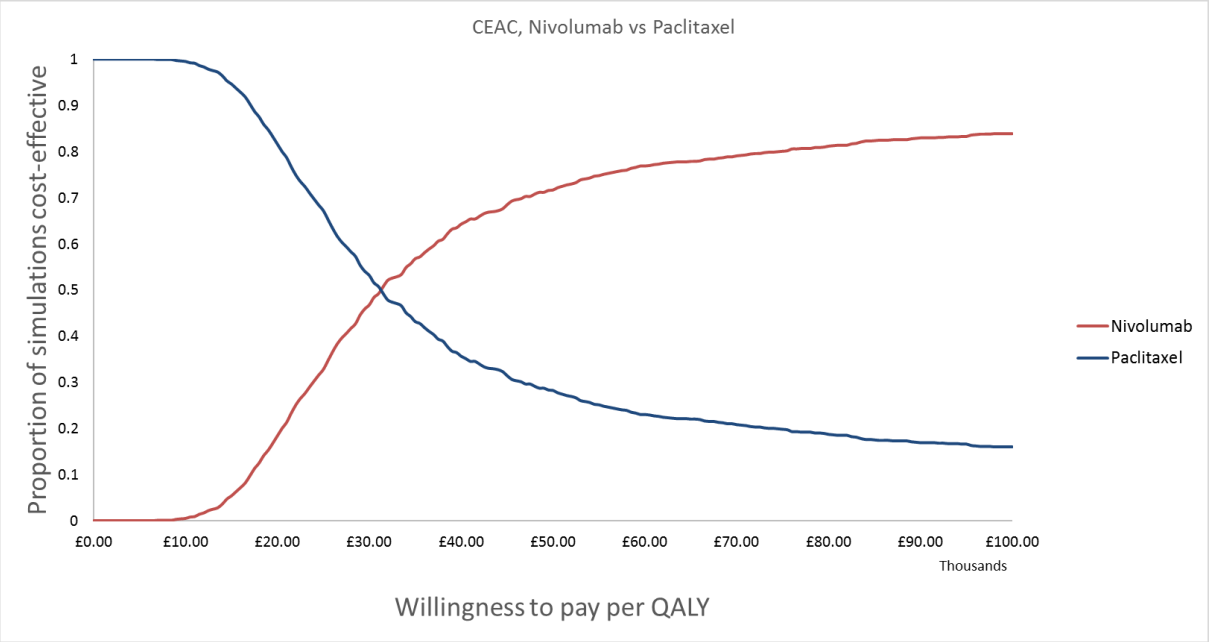
Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Figure 51: Cost-effectiveness acceptability curve: nivolumab (with PAS) versus docetaxel



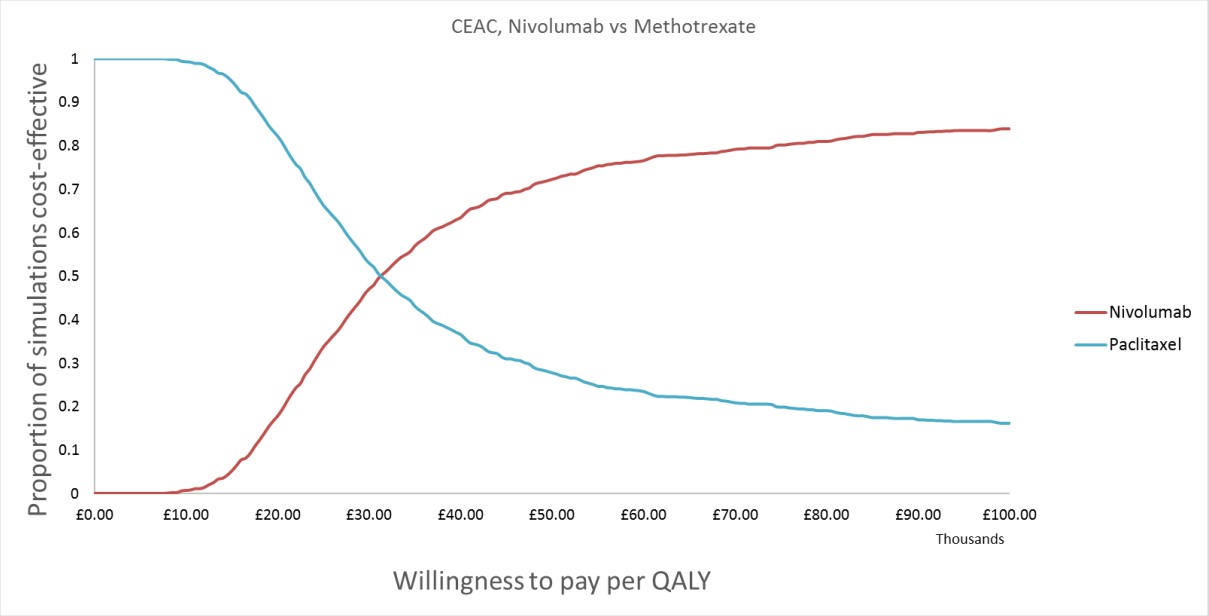
Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Figure 52: Cost-effectiveness acceptability curve: nivolumab (with PAS) versus paclitaxel



Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Figure 53: Cost-effectiveness acceptability curve: nivolumab (with PAS) versus methotrexate



Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

5.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted by varying all parameters for which there were single input values into the model by ±15% of their mean value in order to identify key model drivers. Tornado diagrams showing the top ten drivers of cost-effectiveness in the comparison of nivolumab versus docetaxel, paclitaxel and methotrexate are presented in Figure 54 to Figure 56, respectively, when nivolumab is provided at list price and Figure 57 to Figure 59, respectively, when nivolumab is provided with the PAS. Across Figure 54 to Figure 59 it can be

seen that versus all three comparators the parameter driving the model the most is the utility value utilised for patients in the *progressed disease* state in the nivolumab arm. This utility value is derived directly from EQ-5D-3L data collected in the CheckMate 141 study and is discussed in Section 5.4.1. Following this, the most influential parameters are the treatment frequency of nivolumab and the nivolumab dose. In interpreting model drivers from these tornado diagrams it should be noted that the parametric distributions chosen to model OS and TTD with nivolumab in particular were also key model drivers. However, their impact was not captured by the deterministic sensitivity analysis and was instead explored in scenario analyses.

Figure 54: Tornado diagram of the ten most influential parameters: nivolumab versus docetaxel (without PAS for nivolumab)

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

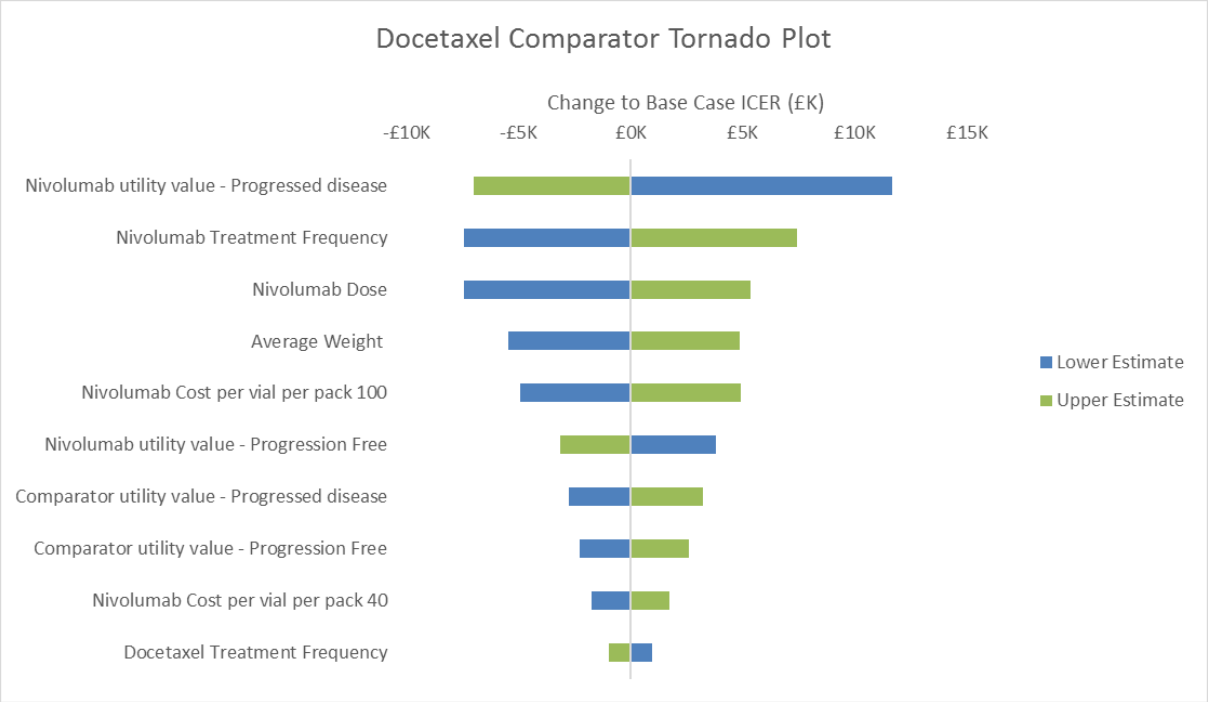
Figure 55: Tornado diagram of the ten most influential parameters: nivolumab versus paclitaxel (without PAS for nivolumab)

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

Figure 56: Tornado diagram of the ten most influential parameters: nivolumab versus methotrexate (without PAS for nivolumab)

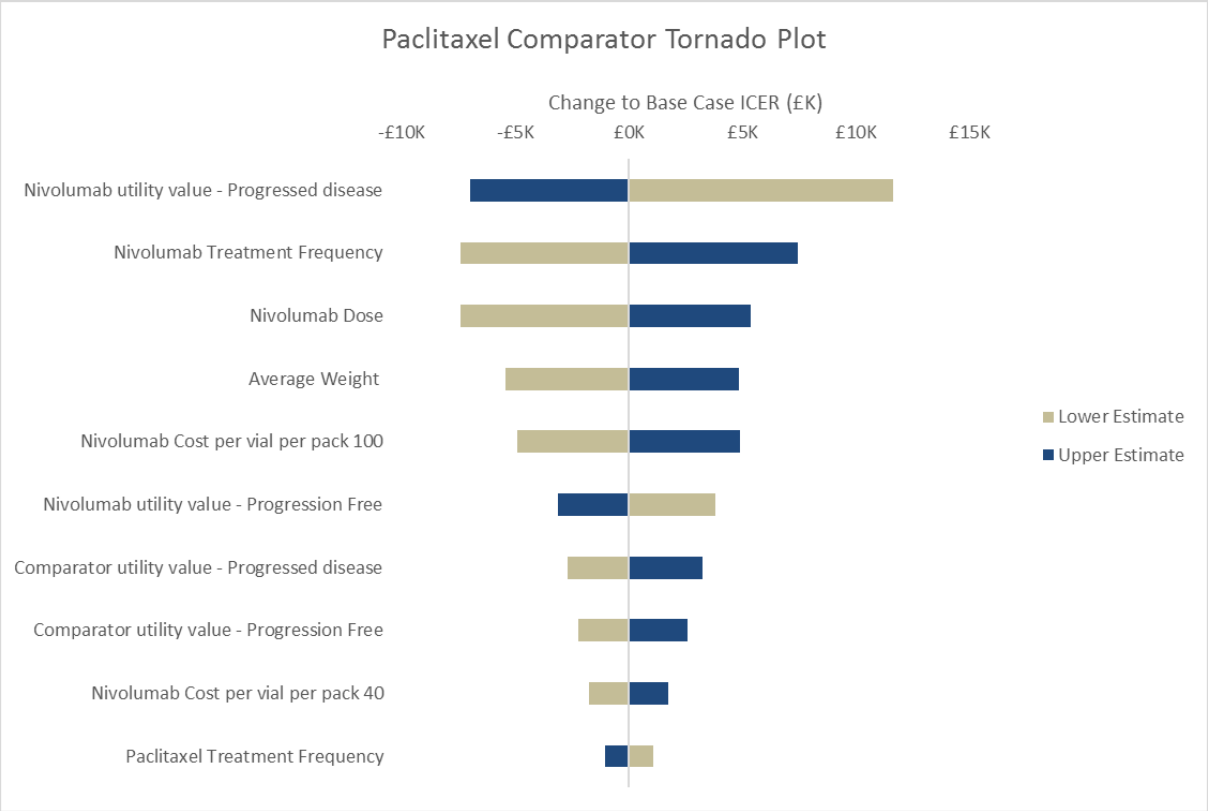
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

Figure 57: Tornado diagram of the ten most influential parameters: nivolumab versus docetaxel (with PAS for nivolumab)



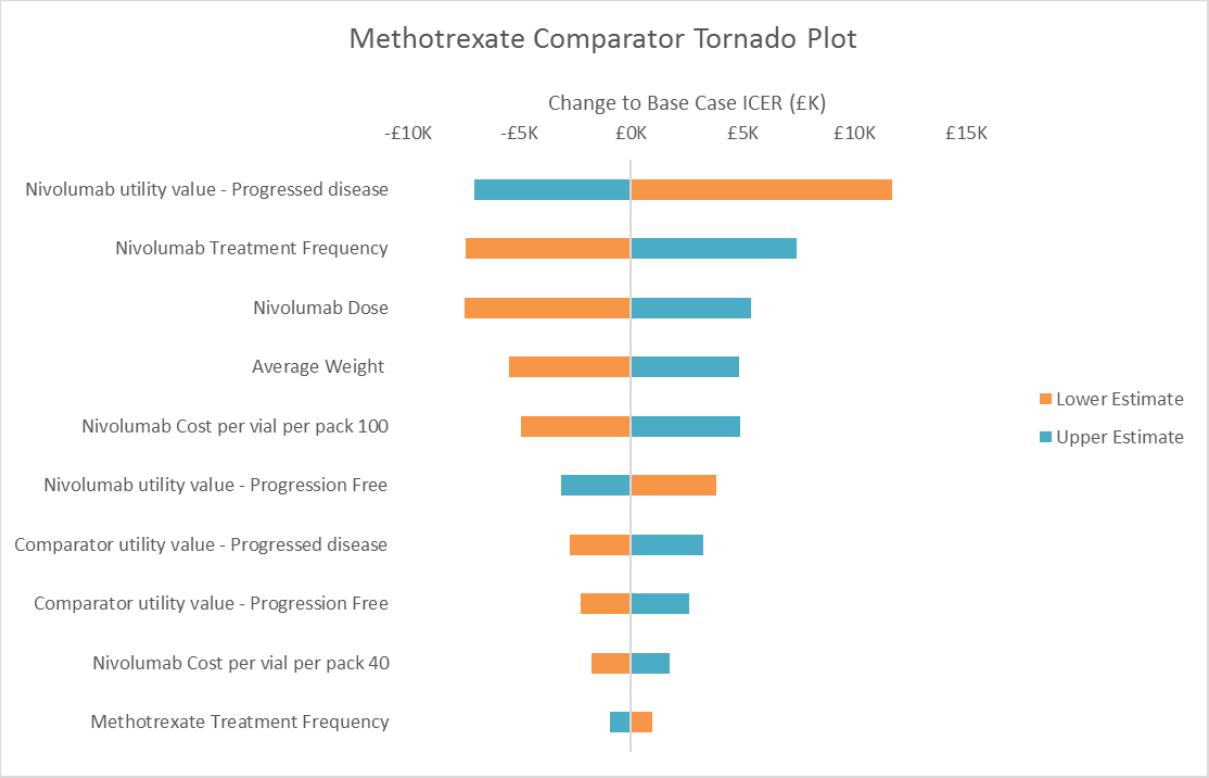
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

Figure 58: Tornado diagram of the ten most influential parameters: nivolumab versus paclitaxel (with PAS for nivolumab)



Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

Figure 59: Tornado diagram of the ten most influential parameters: nivolumab versus methotrexate (with PAS for nivolumab)



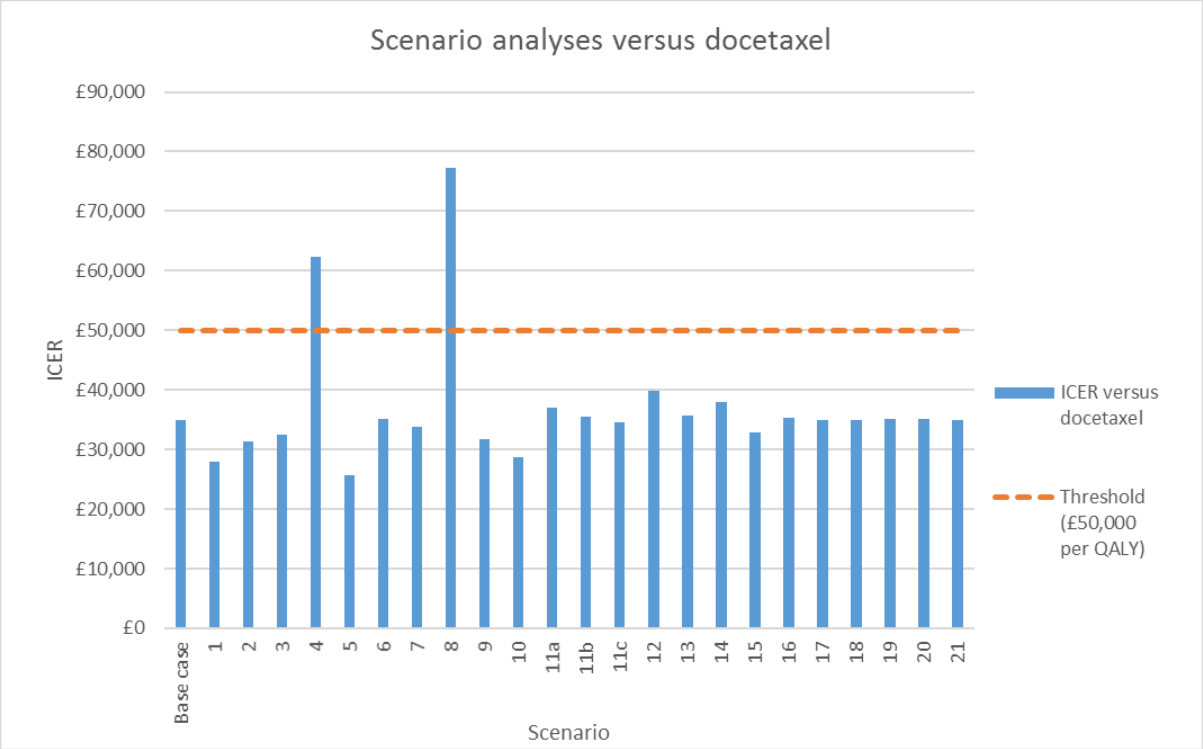
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

5.8.3 Scenario analysis

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis, as listed in Table 52. Scenarios exploring alternative clinical stopping rules (Scenarios 1–3), alternative parametric survival distributions (Scenarios 4–9), the use of PFS to model time on treatment (Scenario 10), and alternative time horizons (Scenario 11a–c) are described in full below, with and without the confidential PAS discount applied for nivolumab. A summary of incremental results for Scenarios 12–21 is presented thereafter (with and without PAS for nivolumab).

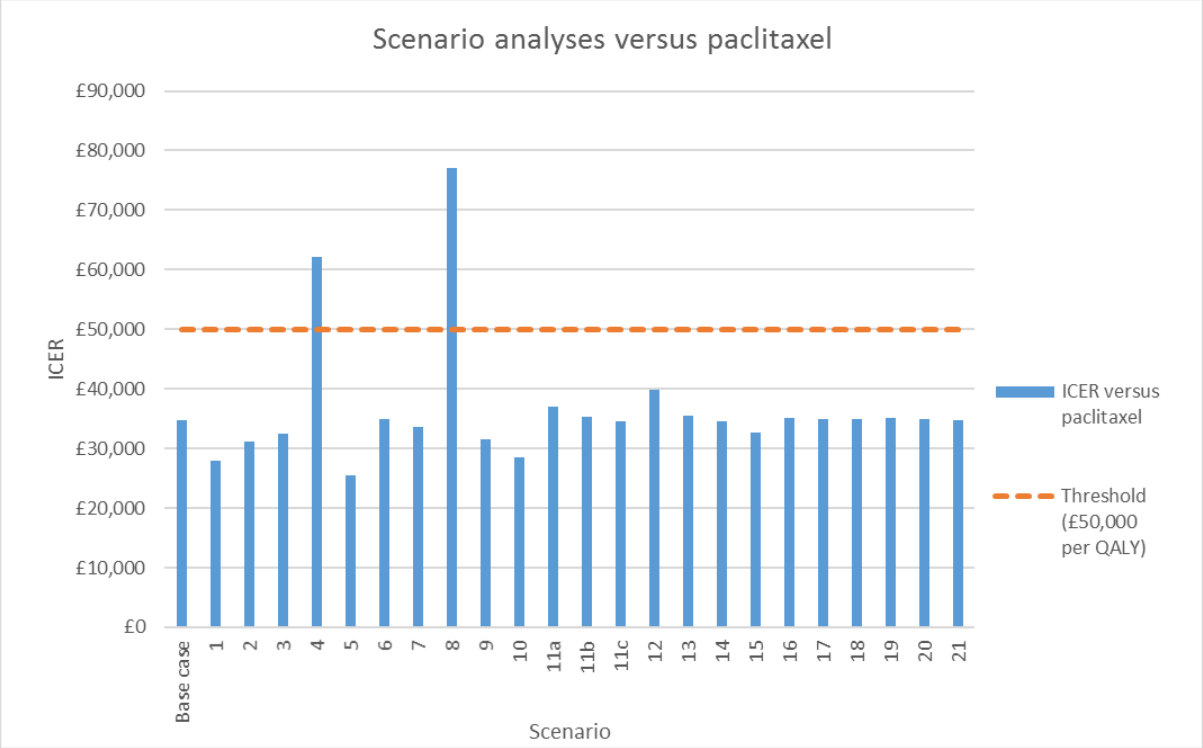
A summary of results from all scenario analyses conducted are presented in Figure 60, Figure 61 and Figure 62 for nivolumab versus each of docetaxel, paclitaxel and methotrexate, respectively, with the confidential PAS discount applied for nivolumab.

Figure 60: Summary of results from scenario analyses (Scenarios 1–21): nivolumab versus docetaxel



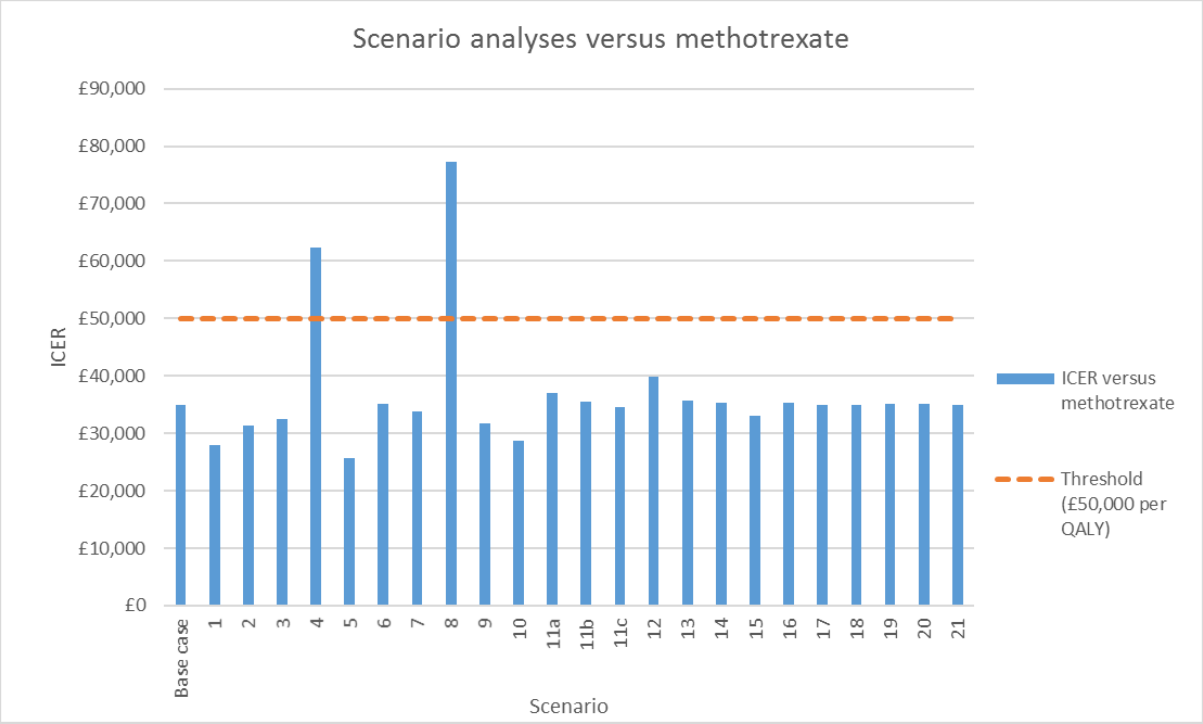
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Figure 61: Summary of results from scenario analyses (Scenarios 1–21): nivolumab versus paclitaxel



Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Figure 62: Summary of results from scenario analyses (Scenarios 1–21): nivolumab versus methotrexate



Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Scenarios 1, 2 and 3 – alternative clinical stopping rules

In the base case analysis, the duration of treatment in the model was based on extrapolated TTD data from the CheckMate 141 trial (see Section 5.2.4). This approach was chosen for the base case analysis rather than using PFS in order to more accurately reflect treatment duration in the trial and to account for the fact that patients in the nivolumab arm were permitted to continue treatment beyond disease progression (see Section 4.7.2).

In addition to this base case, clinical stopping rules were explored in scenario analyses (see Section 5.8.3), to reflect the possibility that, due to the unique mechanism of action of immune-checkpoint inhibitors in restoring anti-tumour immunity, it may be feasible to stop treatment with nivolumab for patients who have not yet progressed and exhibit a durable response and maintenance of clinical benefit. Evidence to support the stopping of treatment for patients who are responding to nivolumab is available from the CheckMate 003 trial in which treatment was continued up to 96 weeks.[106] Ongoing responses after treatment cessation were observed in this trial for patients with advanced NSCLC who had completed 96 weeks of therapy with nivolumab (see Figure 22). In addition, clinical stopping rules have been explored as part of other appraisals by NICE for nivolumab.[19, 20] Further validation to support the use of a clinical stopping rule was sought at an advisory board, at which clinicians stated that patients would be unlikely to receive treatment with nivolumab beyond a maximum of 3 years.[6] Scenario analyses were therefore conducted to explore the impact on the cost-effectiveness of nivolumab of stopping treatment after 1, 2 or 3 years for patients who have yet to discontinue initial therapy. This was implemented in the model by discontinuing all patients who were still receiving treatment at the specified time-point (1, 2 or 3 years), with all other parameters remaining the same.

The incremental costs and QALYs for nivolumab (without PAS) versus each of docetaxel, paclitaxel and methotrexate are presented in Table 65 for stopping rules imposed at years 1, 2 and 3, and in Table 66 with the confidential PAS discount applied to nivolumab. The introduction

of stopping rules was seen to have a notable impact in reducing the incremental costs of nivolumab, resulting in reduced ICERs versus the base case.

Table 65: Scenarios 1–3: clinical stopping rule – 1, 2 and 3 years (without PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: time on treatment based on extrapolated TTD							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 1: clinical stopping rule – 1 year							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 2: clinical stopping rule – 2 years							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 3: clinical stopping rule – 3 years							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years; TTD: time to discontinuation.

Table 66: Scenarios 1–3: clinical stopping rule – 1, 2 and 3 years (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: time on treatment based on extrapolated TTD							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908
Scenario 1: clinical stopping rule – 1 year							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£28,029
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£27,905
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£28,035
Scenario 2: clinical stopping rule – 2 years							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£31,300
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£31,175
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£31,306
Scenario 3: clinical stopping rule – 3 years							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£32,569
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£32,444
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£32,575

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years; TTD: time to discontinuation.

Scenarios 4–5 – Alternative survival distribution for OS: Weibull (pessimistic scenario) and 1-spline odds (optimistic scenario)

As described in Section 5.3, the cost-effectiveness of nivolumab versus each comparator in the base case was assessed using a lognormal distribution. In order to fully characterise the range of ICERs that might result from the choice of OS distributions, scenario analyses were conducted in which a more pessimistic and a more optimistic survival distribution was chosen. Selected distributions for PFS and TTD remained as per the base case analysis in these scenario analysis.

- **Scenario 4 – pessimistic scenario:** The Weibull distribution presented a more pessimistic survival distribution for both nivolumab and comparators and the choice of the Weibull curve for OS for both treatment arms of the model is therefore presented here as a scenario analysis.
- **Scenario 5 – optimistic scenario**: The 1-spline odds distribution was selected as the distribution for an optimistic scenario on the basis that it produced the highest estimated mean OS for nivolumab (23.4 months; versus 8.9 months for IC).

The results of these scenario analyses for nivolumab (without PAS) versus each of docetaxel, paclitaxel and methotrexate are presented in Table 67, and in Table 68 with the confidential PAS

discount applied to nivolumab. Using the Weibull distribution for OS was seen to result in a considerable increase in the ICERs for nivolumab versus comparator therapies compared to the base case. However, as noted earlier in Section 5.3.2, the use of a Weibull distribution introduced logically implausible relationships between TTD, PFS and OS at later time points. Furthermore, the long-term projections using the Weibull distribution provides a much lower estimate of clinical benefit with nivolumab than has been observed in other trials with comparable patient populations (see Figure 27 for absolute estimates and Figure 28 for conditional estimates). As would be expected, when using the more optimistic 1-spline odds distribution for OS, the ICERs for nivolumab versus comparator therapies were considerably reduced compared to the base case.

Table 67: Scenarios 4–5: alternative survival distribution for OS – Weibull (pessimistic) and 1-spline odds (optimistic) (without PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: lognormal							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 4: pessimistic survival distribution for OS – Weibull							
Nivolumab	[redacted]	0.88	[redacted]				
Docetaxel	12,315	0.55	0.31	[redacted]	0.33	[redacted]	[redacted]
Paclitaxel	12,379	0.55	0.31	[redacted]	0.33	[redacted]	[redacted]
Methotrexate	12,312	0.55	0.31	[redacted]	0.33	[redacted]	[redacted]
Scenario 5: optimistic survival distribution for OS – 1-spline odds							
Nivolumab	[redacted]	1.68	[redacted]				
Docetaxel	12,607	0.68	0.39	[redacted]	1.00	[redacted]	[redacted]
Paclitaxel	12,672	0.68	0.39	[redacted]	1.00	[redacted]	[redacted]
Methotrexate	12,604	0.68	0.39	[redacted]	1.00	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 68: Scenario 4–5: alternative survival distribution for OS – Weibull (pessimistic) and 1-spline odds (optimistic) (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: lognormal							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908
Scenario 4: pessimistic survival distribution for OS – Weibull							
Nivolumab	[redacted]	0.88	[redacted]				
Docetaxel	12,315	0.55	0.31	[redacted]	0.33	[redacted]	£62,388
Paclitaxel	12,379	0.55	0.31	[redacted]	0.33	[redacted]	£62,156
Methotrexate	12,312	0.55	0.31	[redacted]	0.33	[redacted]	£62,399
Scenario 5: optimistic survival distribution for OS – 1-spline odds							
Nivolumab	[redacted]	1.68	[redacted]				
Docetaxel	12,607	0.68	0.39	[redacted]	1.00	[redacted]	£25,650
Paclitaxel	12,672	0.68	0.39	[redacted]	1.00	[redacted]	£25,562
Methotrexate	12,604	0.68	0.39	[redacted]	1.00	[redacted]	£25,654

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Scenarios 6–7 – Alternative survival distribution for PFS: Gamma (pessimistic scenario) and 2-spline odds (optimistic scenario)

The impact on cost-effectiveness results of using a distribution for PFS that represented either a more pessimistic or a more optimistic extrapolation of PFS with nivolumab was explored in scenario analyses. Selected distributions for OS and TTD remained as per the base case analysis in these scenario analyses.

- **Scenario 6 – pessimistic scenario:** The Gamma model was selected as this was found to be the distribution predicting the lowest mean PFS with nivolumab (4.2 months for nivolumab versus 3.5 months for comparators)
- **Scenario 7 – optimistic scenario**: The 2-spline odds distribution was selected as this was found to be the distribution predicting the highest mean PFS with nivolumab (9.2 months for nivolumab versus 3.7 months for comparators))

The results of these scenario analyses for nivolumab (without PAS) versus each of docetaxel, paclitaxel and methotrexate are presented in Table 69, and in Table 70 with the confidential PAS discount applied to nivolumab. Using either distribution for PFS was seen to have little impact on the ICERs for nivolumab versus comparator therapies compared to the base case analysis.

Table 69: Scenarios 6–7: alternative survival distribution for PFS – Gamma (pessimistic) and 2-spline odds (optimistic) (without PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: generalised gamma							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 6: pessimistic survival distribution for PFS – Gamma							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,537	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,601	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,534	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 7: optimistic survival distribution for PFS – 2-spline odds							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,544	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,608	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,541	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 70: Scenarios 6–7: alternative survival distribution for PFS – Gamma (pessimistic) and 2-spline odds (optimistic) (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: generalised gamma							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908
Scenario 6: pessimistic survival distribution for PFS – Gamma							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,537	0.65	0.37	[redacted]	0.68	[redacted]	£35,042
Paclitaxel	12,601	0.65	0.37	[redacted]	0.68	[redacted]	£34,917
Methotrexate	12,534	0.65	0.37	[redacted]	0.68	[redacted]	£35,048
Scenario 7: optimistic survival distribution for PFS – 2-spline odds							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,544	0.65	0.37	[redacted]	0.68	[redacted]	£33,723
Paclitaxel	12,608	0.65	0.37	[redacted]	0.68	[redacted]	£33,604
Methotrexate	12,541	0.65	0.37	[redacted]	0.68	[redacted]	£33,729

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Scenarios 8–9 – Alternative survival distribution for TTD: 2-spline odds (pessimistic) and Gamma (optimistic)

As described in Section 5.3.4.1, scenario analyses were conducted to explore the impact of using a parametric distribution for TTD that provided either a much higher or lower estimate for mean TTD with nivolumab compared to that resulting from the base case distribution. A higher estimate of mean TTD represents a more pessimistic scenario with regards to the ICER for nivolumab versus comparators due to the increased drug costs associated with prolonged treatment. Selected distributions for OS and PFS remained as per the base case analysis in this scenario analysis.

- **Scenario 8 – pessimistic scenario:** The 2-spline odds distribution was selected as this was found to predict the highest mean TTD for nivolumab ([redacted]). As noted in Section 5.3.4.1, the 2-spline odds distribution is considered to be clinically wholly unrealistic based on expert clinician feedback in terms of the predicted treatment duration with nivolumab. Furthermore, it predicts patients who are no longer alive to still be receiving nivolumab (i.e. the extrapolated TTD curve for nivolumab reaches a point at which it is higher than the base case OS curve for nivolumab). This scenario was included as an example of the impact of an extreme assumption for TTD with nivolumab.
- **Scenario 9 – optimistic scenario:** The Gamma distribution was selected as this predicted a mean TTD for nivolumab ([redacted]) that was lower than the base case loglogistic curve ([redacted]) and was amongst the lowest of all distributions explored.

The results of these scenario analyses for nivolumab (without PAS) versus each of docetaxel, paclitaxel and methotrexate are presented in Table 71, and in Table 72 with the confidential PAS discount applied to nivolumab. Choosing a distribution for TTD that resulted in a long mean TTD for nivolumab resulted in a considerable increase to the ICERs for nivolumab relative to the base case analysis. However, when interpreting the results of this scenario analysis the clinical implausibility of the predicted length of TTD with nivolumab, in addition to the logical paradox versus the OS distribution introduced by using this curve for TTD, should be considered. Conversely, using a distribution for TTD that predicted shorter TTD with nivolumab compared to the base case resulted in a lowering of the ICERs for nivolumab versus comparator therapies, as would be expected.

Table 71: Scenario 8–9: alternative survival distribution for TTD – 2-spline odds (pessimistic) and Gamma (optimistic) (without PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: loglogistic							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 8: pessimistic survival distribution for TTD – 2-spline odds							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,291	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,351	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,288	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 9: optimistic survival distribution for TTD – Gamma							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,226	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,285	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,224	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 72: Scenarios 8–9: alternative survival distribution for TTD – 2-spline odds (pessimistic) and Gamma (optimistic) (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: loglogistic							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908
Scenario 8: pessimistic survival distribution for TTD – 2-spline odds							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,291	0.65	0.37	[redacted]	0.68	[redacted]	£77,227
Paclitaxel	12,351	0.65	0.37	[redacted]	0.68	[redacted]	£77,111
Methotrexate	12,288	0.65	0.37	[redacted]	0.68	[redacted]	£77,232
Scenario 9: optimistic survival distribution for TTD – Gamma							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,226	0.65	0.37	[redacted]	0.68	[redacted]	£31,631
Paclitaxel	12,285	0.65	0.37	[redacted]	0.68	[redacted]	£31,518
Methotrexate	12,224	0.65	0.37	[redacted]	0.68	[redacted]	£31,636

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Scenario 10 – Modelling time on treatment using PFS rather than TTD

To explore the impact of assuming no treatment beyond progression with nivolumab or the comparator therapies, a scenario analysis was conducted in which time on treatment was modelled based on the PFS curves rather than the TTD curves used in the base case.

The results of this scenario analysis for nivolumab (without PAS) versus each of docetaxel, paclitaxel and methotrexate are presented in Table 73, and in Table 74 with the confidential PAS discount applied to nivolumab. Assuming no treatment beyond progression results in a reduction to the ICERs for nivolumab versus comparator therapies compared to the base case. This is a result of the reduced time patients spend on nivolumab therapy and hence a reduction in drug costs accrued in this arm of the model relative to the base case analysis.

Table 73: Scenario 10: modelling time on treatment using PFS (without PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: time on treatment based on extrapolated TTD							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 10: time on treatment based on extrapolated PFS							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,510	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,574	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,507	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; QALYs: quality-adjusted life years; TTD: time to discontinuation.

Table 74: Scenario 10: modelling time on treatment using PFS (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: time on treatment based on extrapolated TTD							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908
Scenario 10: time on treatment based on extrapolated PFS							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,510	0.65	0.37	[redacted]	0.68	[redacted]	£28,705
Paclitaxel	12,574	0.65	0.37	[redacted]	0.68	[redacted]	£28,582
Methotrexate	12,507	0.65	0.37	[redacted]	0.68	[redacted]	£28,711

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; QALYs: quality-adjusted life years; TTD: time to discontinuation.

Scenario 11a–c – alternative time horizons

The base case analysis used a time horizon of 20 years. The impact of assuming shorter and longer time horizons was explored in a scenario analysis. Time horizons of a) 10 years, b) 15 years and c) 25 years were tested in order to determine the impact of assuming both shorter and longer time horizons than the base case. In all scenarios, all other settings were as per the base case analysis.

The results of these scenario analysis for nivolumab (without PAS) versus each of docetaxel, paclitaxel and methotrexate are presented in Table 75, and in Table 76 with the confidential PAS discount applied to nivolumab. Varying the time horizon between 10 years and 25 years was seen to have a relatively minimal impact on the ICERs for nivolumab versus comparator therapies.

Table 75: Scenario 11a–c: using alternative time horizons (without PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: 20 years							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Scenario 11a: 10 years							
Nivolumab	[redacted]	1.27	[redacted]				
Docetaxel	12,532	0.65	0.37	[redacted]	0.62	[redacted]	[redacted]
Paclitaxel	12,597	0.65	0.37	[redacted]	0.62	[redacted]	[redacted]
Methotrexate	12,529	0.65	0.37	[redacted]	0.62	[redacted]	[redacted]
Scenario 11b: 15 years							
Nivolumab	[redacted]	1.31	[redacted]				
Docetaxel	12,537	0.65	0.37	[redacted]	0.66	[redacted]	[redacted]
Paclitaxel	12,602	0.65	0.37	[redacted]	0.66	[redacted]	[redacted]
Methotrexate	12,534	0.65	0.37	[redacted]	0.66	[redacted]	[redacted]
Scenario 11c: 25 years							
Nivolumab	[redacted]	1.34	[redacted]				
Docetaxel	12,539	0.65	0.37	[redacted]	0.69	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.69	[redacted]	[redacted]
Methotrexate	12,536	0.65	0.37	[redacted]	0.69	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; OS: overall survival; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 76: Scenario 11a–c: using alternative time horizons (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALYs)
Base case: 20 years							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908
Scenario 11a: 10 years							
Nivolumab	[redacted]	1.27	[redacted]				
Docetaxel	12,532	0.65	0.37	[redacted]	0.62	[redacted]	£37,081
Paclitaxel	12,597	0.65	0.37	[redacted]	0.62	[redacted]	£36,946
Methotrexate	12,529	0.65	0.37	[redacted]	0.62	[redacted]	£37,088
Scenario 11b: 15 years							
Nivolumab	[redacted]	1.31	[redacted]				
Docetaxel	12,537	0.65	0.37	[redacted]	0.66	[redacted]	£35,524
Paclitaxel	12,602	0.65	0.37	[redacted]	0.66	[redacted]	£35,396
Methotrexate	12,534	0.65	0.37	[redacted]	0.66	[redacted]	£35,530
Scenario 11c: 25 years							
Nivolumab	[redacted]	1.34	[redacted]				
Docetaxel	12,539	0.65	0.37	[redacted]	0.69	[redacted]	£34,607
Paclitaxel	12,603	0.65	0.37	[redacted]	0.69	[redacted]	£34,484
Methotrexate	12,536	0.65	0.37	[redacted]	0.69	[redacted]	£34,613

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Scenarios 12–21 – summary of incremental results

Scenario analyses were also conducted in which the impact of varying assumptions in the model were explored (see Section 5.6.2). These related to utilities used in the model (Scenarios 12–13), treatment dosing and related patient characteristics (Scenarios 14–16 and 20–21), subsequent systemic therapies (Scenarios 17–18), and terminal care costs (Scenario 19). The incremental results for each of these analyses are presented in Table 77 (without PAS for nivolumab) and in Table 78 (with PAS).

Table 77: Scenarios 12–21: Incremental results for nivolumab versus comparators (without PAS for nivolumab)

#	Scenario	Incremental results for nivolumab versus:								
		Docetaxel			Paclitaxel			Methotrexate		
		Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)	Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)	Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)
	Base case analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	Using health-state utilities from the overall trial population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	No disutility due to AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	Docetaxel 75 mg/m^2 Q3W dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	Vial sharing included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	100% dose intensity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	Reduced % of patients receiving subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	No subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	No terminal care cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	Using average weight and BSA from the overall trial population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	Using average BSA from UK cancer patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AEs: adverse events; BSA: body surface area; ICER: incremental cost-effectiveness ratio; Q3W: once every three weeks; QALYs: quality-adjusted life years.

Table 78: Scenarios 12–21: Incremental results for nivolumab versus comparators (with PAS for nivolumab)

#	Scenario	Incremental results for nivolumab versus:								
		Docetaxel			Paclitaxel			Methotrexate		
		Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)	Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)	Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)
	Base case analysis	[redacted]	[redacted]	£34,902	[redacted]	[redacted]	£34,777	[redacted]	[redacted]	£34,908
12	Using health-state utilities from the overall trial population	[redacted]	[redacted]	£39,910	[redacted]	[redacted]	£39,767	[redacted]	[redacted]	£39,917
13	No disutility due to AEs	[redacted]	[redacted]	£35,688	[redacted]	[redacted]	£35,561	[redacted]	[redacted]	£35,694
14	Docetaxel 75 mg/m^2 Q3W dose	[redacted]	[redacted]	£37,978	[redacted]	[redacted]	£34,493	[redacted]	[redacted]	£35,249
15	Vial sharing included	[redacted]	[redacted]	£32,866	[redacted]	[redacted]	£32,703	[redacted]	[redacted]	£32,995
16	100% dose intensity	[redacted]	[redacted]	£35,327	[redacted]	[redacted]	£35,146	[redacted]	[redacted]	£35,333
17	Reduced % of patients receiving subsequent systemic therapy	[redacted]	[redacted]	£35,006	[redacted]	[redacted]	£34,882	[redacted]	[redacted]	£35,013
18	No subsequent systemic therapy	[redacted]	[redacted]	£35,012	[redacted]	[redacted]	£34,887	[redacted]	[redacted]	£35,019
19	No terminal care cost	[redacted]	[redacted]	£35,206	[redacted]	[redacted]	£35,081	[redacted]	[redacted]	£35,212
20	Using average weight and BSA from the overall trial population	[redacted]	[redacted]	£35,116	[redacted]	[redacted]	£34,994	[redacted]	[redacted]	£35,122
21	Using average BSA from UK cancer patients	[redacted]	[redacted]	£34,902	[redacted]	[redacted]	£34,783	[redacted]	[redacted]	£34,908

Abbreviations: AEs: adverse events; BSA: body surface area; ICER: incremental cost-effectiveness ratio; Q3W: once every three weeks; QALYs: quality-adjusted life years.

5.8.4 Summary of sensitivity analyses results

Results of sensitivity analyses demonstrated the cost-effectiveness results to be robust to the combined distributional uncertainty across model parameters (PSA) and to the majority of changes to modelling approach that were explored in scenario analyses. Scenario analyses clearly demonstrated that the model results were sensitive to the choice of distribution for OS and TTD, though results were relatively insensitive to the choice of distribution for PFS. Use of a pessimistic OS distribution (Weibull) that reduced the expected survival benefit of both nivolumab and the comparators resulted in substantial increases to the ICERs, whilst use of optimistic distributions had the opposite effect. For the reasons explained earlier, the choice of base case distribution for OS was considered the most appropriate based on considerations of statistical fit, clinical plausibility and validation exercises; nonetheless, the scenario analyses do highlight the impact of uncertainty in long-term survival outcomes with nivolumab and comparators in R/M SCCHN. Similarly, when a pessimistic (in terms of ICERs for nivolumab) distribution for TTD was applied this was seen to substantially raise the ICERs, whilst choice of an optimistic TTD curve, or indeed assuming no treatment beyond progression and setting TTD equal to PFS, considerably reduced the ICERs. The pessimistic TTD distribution was presented as an exploratory scenario and highlights the high potential impact of any uncertainty in TTD; however, the long mean TTD with nivolumab predicted in this scenario is considered clinically wholly implausible.

Deterministic sensitivity analysis demonstrated that, apart from the choice of distribution for OS and TTD, the key model drivers were the utility value for *progressed disease* for patients treated with nivolumab and the treatment frequency with nivolumab. Varying these parameters by ±15% was seen to result in changes to the base case ICERs ranging from reductions of less than £10,000 per QALY to increases of less than £15,000, respectively (with PAS for nivolumab). It should be noted, however, that a scenario analysis in which health state utility values were set equal between treatment arms as an alternative approach to modelling health state utilities resulted in relatively modest increases to the base case ICERs.

5.9 Subgroup analysis

No subgroup analyses are presented as a part of the cost-effectiveness analysis.

5.10 Validation

As described in Section 5.3, there is a paucity of long-term data for survival outcomes in patients with R/M SCCHN receiving either nivolumab or comparator therapies. Registry sources (the SEER database and the UK OCIU) were considered as potential data sources for validation of long-term extrapolations; however, data for a patient population sufficiently analogous to that investigated in CheckMate 141 and considered in this submission were not available meaning that these data sources could not be used for validation.

Validation of the survival models used in the base case analysis was therefore performed using the following considerations:

- Comparison of nivolumab OS outcomes predicted by chosen survival distributions to long-term OS outcomes observed with nivolumab in clinical trials in the advanced squamous NSCLC population. In light of the lack of any long-term data in R/M SCCHN, this population was considered the most appropriate for comparison based on similarities in tumour histology and typical patient characteristics (e.g. age, smoking status, alcohol status, co-

morbidities).[19] Clinical feedback sought as part of model development supported the use of data for nivolumab from squamous NSCLC as validation for longer-term survival outcomes in the absence of any other data.

- Expert clinical opinion regarding expected OS with comparator therapies used in current clinical practice
- Expert clinical opinion regarding expected mean PFS and TTD
- Consideration of the relationship between OS, PFS and TTD under selected distributions:
    - Whether the choice of distributions introduced any logical inconsistencies such as OS falling below PFS or TTD
    - Whether the relationship between predicted mean PFS and TTD appeared plausible
- Whether the selected OS curve introduced any clinical implausibility in terms of the probability of death for R/M SCCHN patients receiving either nivolumab or comparator therapies falling to a level below the probability of death of the general age-matched population.

Consideration of the above criteria are presented in Section 5.3 in relation to the discussion of the selection of the base case curves. In summary, the base case choice of curves for OS (lognormal), PFS (generalised-gamma) and TTD (loglogistic) was considered valid based on the following:

- Predicted OS for nivolumab or comparator therapies was aligned to longer-term data from the advanced squamous NSCLC population (for nivolumab) and expert clinical opinion (for comparator therapies) – see Table 28
- Predicted OS with nivolumab or comparator therapies did not fall below the PFS or TTD curves at any point over the 20-year time horizon
- Predicted probabilities of death for patients receiving nivolumab or comparator therapies did not fall below age-matched general population mortality at any time point in the 20-year time horizon
- Mean TTD ([redacted]) and mean PFS (4.6 months) on nivolumab had a clinically plausible relationship, [redacted]. The predicted mean TTD and the relative lengths of PFS and TTD were aligned to expert clinical opinion.

In addition to the validation of survival outcomes, expert clinical opinion was sought to validate the following model inputs:

- Relevant adverse events and their associated disutilities
- Disease management resource use for SCCHN
- Equivalence of efficacy between comparators
- Equivalence of efficacy of docetaxel when used at the trial dosing frequency and at clinical practice dosing frequency

5.11 Interpretation and conclusions of economic evidence

When interpreting and concluding your economic evidence, consider the following:

1. Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

This is the first economic evaluation undertaken for nivolumab in an R/M SCCHN population. There is no published evidence for a direct comparison.

2. Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?

Yes, the economic evaluation considers patients with R/M SCCHN who have progressed after platinum-based therapy. This population reflects patients enrolled in CheckMate 141 and is in line with the final NICE scope.

3. How relevant (generalisable) is the analysis to clinical practice in England?

The analysis is likely to be directly applicable to clinical practice in England. Resource use assumptions have been validated with input from UK clinicians and costs were sourced from UK sources (e.g. NHS Reference Costs, BNF or previous NICE technology appraisals) where possible. Weight and BSA inputs used in the economic model were taken from the European population of patients in the CheckMate 141 trial and validated against UK-specific BSA data.

The patient population in CheckMate 141 can be considered reflective of the patient population in the UK, supporting the relevance of the clinical outcomes observed in the trial to the anticipated treatment effects in UK practice (see Section 4.13.3). A limitation of the generalisability of the trial outcomes that inform the clinical effectiveness estimates in the model is the fact that the CheckMate 141 trial used an IC comparator arm that included cetuximab monotherapy, a therapy not used in UK clinical practice or included as a relevant comparator in this appraisal. However, only a small proportion (12%) of patients treated in the IC arm of CheckMate 141 received cetuximab. Paclitaxel, a comparator in UK clinical practice, did not form part of the IC arm in the CheckMate 141 trial which may limit the generalisability of the trial results from the IC arm to that comparator. However, given that paclitaxel belongs to the same class of therapies as docetaxel and that expert clinical feedback supported an assumption of equivalent efficacy between these two therapies, this is not considered an issue in terms of generalisability.

4. What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The economic model is underpinned by patient-level data from the CheckMate 141 trial, which collected data on efficacy, treatment patterns, and quality of life. Survival extrapolation was essential to quantify the survival benefit beyond the trial period. A robust and comprehensive approach was followed during the survival extrapolation to ensure the methods were statistically sound, but also clinically plausible. Attempts to validate modelled outcomes against expected outcomes in real world clinical practice were made despite the paucity of data for comparison. In terms of resource utilisation, all inputs were validated and sourced from UK publications.

A limitation of the cost-effectiveness analysis is that it uses efficacy from the IC arm of the CheckMate 141 study to inform effectiveness estimates for all three comparators in the model (docetaxel, paclitaxel and methotrexate). Whilst there is a lack of published data to support this assumption of equivalence of effectiveness of these therapies in this patient population, clinical feedback was that this assumption was reasonable and that differences in efficacy between these therapies would not be expected in clinical practice. The justification for using efficacy from the IC arm for each comparator was a considered one, based on concern for preserving statistical power and randomisation in the use of results from the CheckMate 141 trial.

5. What further analyses could be carried out to enhance the robustness or completeness of the results?

Extensive scenario analyses were performed and showed the model to be generally robust to the majority of assumptions employed in the base case analysis. These scenario analyses highlighted the considerable impact of the choice of statistical distribution for OS and TTD on model results. There is a lack of published evidence for long-term OS with either nivolumab or comparator therapies and it is clear that to enhance the robustness of the analysis, longer follow-up of trial patients for OS would be beneficial. An updated data cut for OS from the CheckMate 141 trial is anticipated in [redacted]. The exact approach of clinicians in terms of maintaining patients on nivolumab therapy is currently uncertain due to the novel nature of this therapy. Whilst clinical feedback was sought to assess the plausibility of TTD on nivolumab predicted in the base case analysis, it would be important to obtain certainty around the likely optimal treatment duration for patients in clinical practice; in particular, with regards to whether there is a time point beyond which clinical benefit would continue despite stopping treatment.

Conclusion

- The economic model predicts nivolumab to be associated with considerable extension to life for R/M SCCHN patients who have previously progressed on platinum-based therapy, consistent with the primary outcome of the CheckMate 141 trial
- When provided with a PAS, nivolumab is estimated to represent a cost-effective use of NHS resources as an end-of-life medicine, being associated with base case ICERs ranging from £34,777 to £34,908 versus the relevant comparators defined in the NICE scope for this appraisal
- The model results were seen to be robust to the majority of assumptions, as tested in extensive scenario analyses. The choice of distribution for OS and TTD represented the greatest influence on the ICERs for nivolumab; the base case choices of distributions were based on extensive consideration of statistical fit and clinical plausibility

6 Assessment of factors relevant to the NHS and other parties

6.1 Number of patients eligible for treatment in England and Wales

For the analysis of budget impact, the incident number of patients in England and Wales eligible for treatment with nivolumab, as per the anticipated indication for SCCHN, was estimated to be 576 per year (see Figure 63). This analysis was based on a closed cohort; as a result, the number of patients eligible to receive nivolumab was estimated to be 576 each year over the 5-year time horizon.

Figure 63: Eligible population for nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy

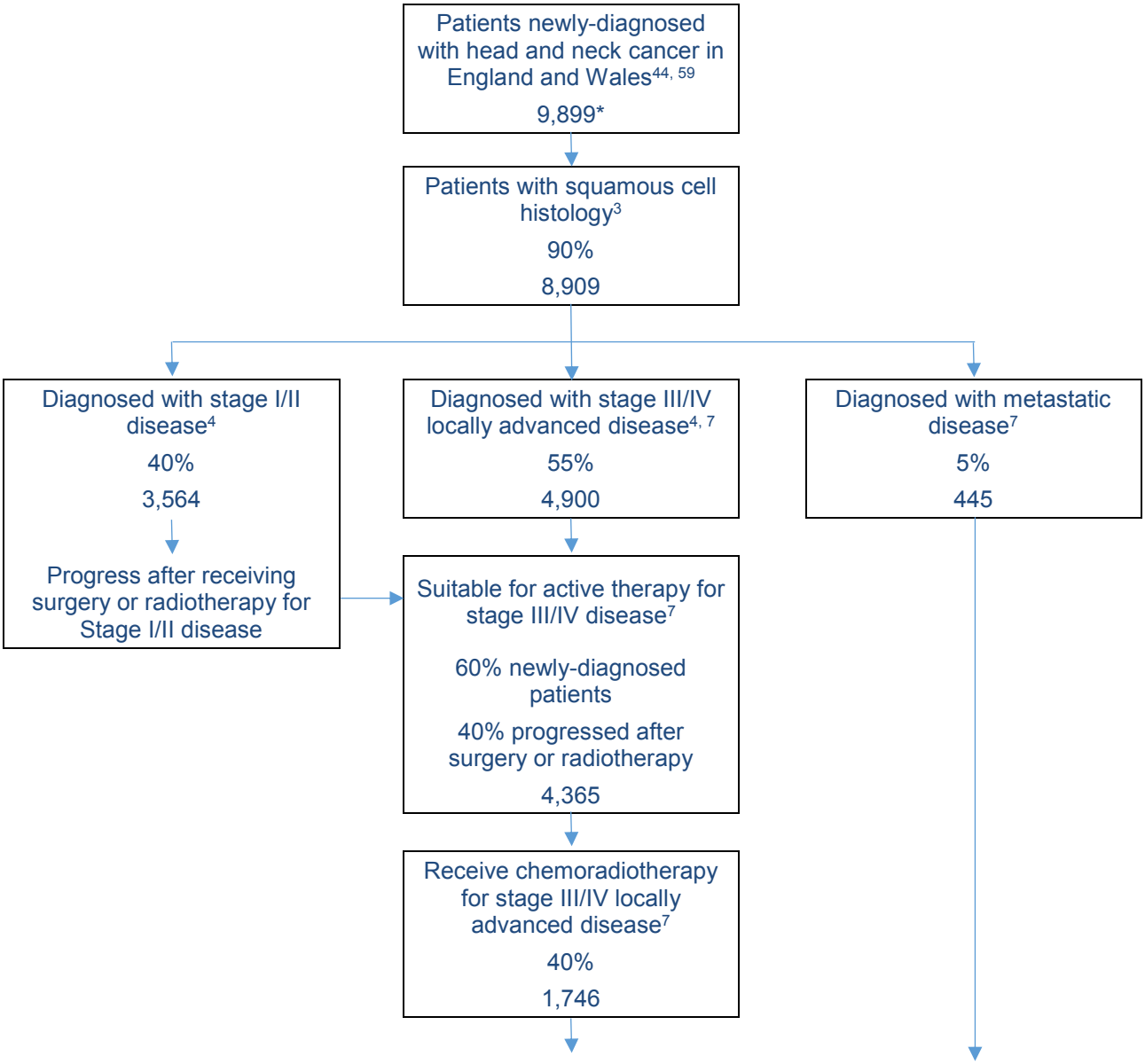
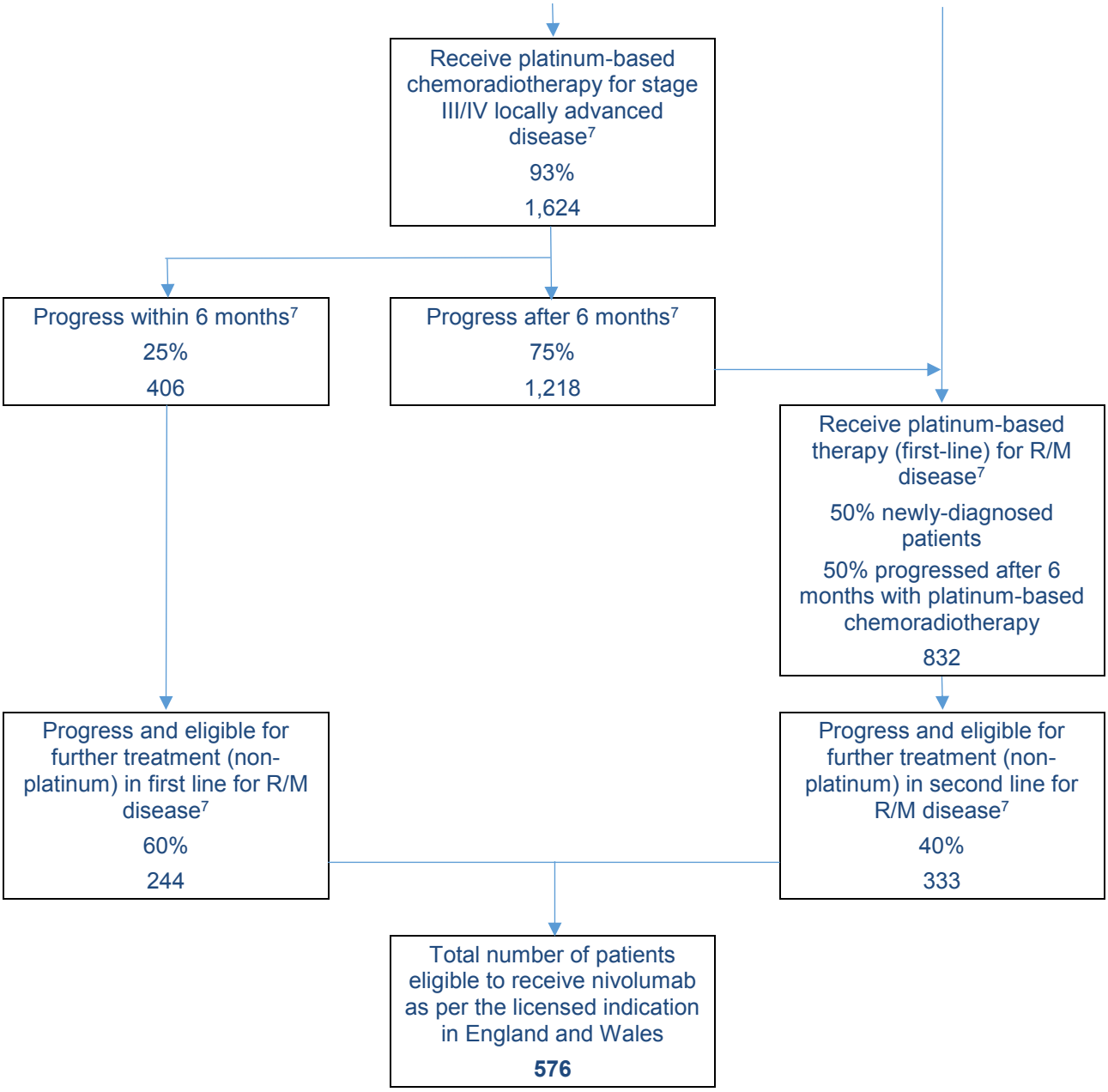


Figure 63 continued.



* Includes cases classified under ICD10 codes: C00 to C14 and C30 to C32.
Individual C00–C97 codes refer to diseases classified as 'malignant neoplasms' by the World Health Organisation in the ICD-10.

Abbreviations: ICD: International Classification of Diseases; N/A: not applicable; R/M: recurrent or metastatic; SCCHN: squamous-cell carcinoma of the head and neck.

6.2 Assumptions made about current treatment options and uptake of technologies

All comparators included in the final scope for this appraisal (docetaxel, paclitaxel and methotrexate) have been considered in the budget impact analysis and are assumed to be equally displaced by the introduction of nivolumab. Market share estimates used in the budget impact analysis are presented in Section 6.3.

6.3 Assumptions made about market share in England and Wales

The proportion of patients receiving each therapy, based on internal market share estimates for patients eligible to receive nivolumab in either the first or second-line R/M SCCHN settings, is presented in Table 79 for the scenario without nivolumab and in Table 80 for the scenario with nivolumab. In total, approximately 244 patients are expected to be eligible to receive first-line therapy in the R/M setting (after platinum-based therapy) and 333 patients are expected to be eligible to receive second-line therapy after having received platinum-based therapy in the first-line R/M setting (see Figure 63).

As described in Section 3.2, the majority of patients with platinum-refractory R/M SCCHN are currently expected to receive treatment with docetaxel, with methotrexate and paclitaxel used to a lesser extent.[5, 7] As the first immune-checkpoint inhibitor that could potentially be made available to patients in the UK, nivolumab is expected to have a market share of [redacted]% in Year 1, rising to [redacted]% in subsequent years, in the first-line R/M setting, and [redacted]% in Year 1, rising to [redacted]% in subsequent years, in the second-line R/M setting.[137]

Table 79: Proportion of patients receiving each therapy – NHS without nivolumab

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
First-line (non-platinum) treatment of R/M SCCHN					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second-line treatment of R/M SCCHN after platinum-based, first-line therapy					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NHS: National Health Service.

Table 80: Proportion of patients receiving each therapy – NHS with nivolumab

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
First-line (non-platinum) treatment of R/M SCCHN					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second-line treatment of R/M SCCHN after platinum-based, first-line therapy					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NHS: National Health Service.

Table 81: Number of patients receiving each therapy – NHS without nivolumab

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NHS: National Health Service.

Table 82: Number of patients receiving each therapy – NHS with nivolumab

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NHS: National Health Service.

6.4 Other significant costs associated with treatment

Costs associated with drug acquisition and administration were included in the budget impact analysis. Annual costs per patient were derived from costs accrued over a 1-year time horizon in the cost-effectiveness analysis described in Section 5.2 and are presented in Table 83. Details of the unit costs for drug acquisition and administration included in this analysis are presented in Section 5.5.2.

The budget impact analysis was conducted with and without the confidential PAS for nivolumab. Details of this PAS are provided in Section 2.3.

Table 83: Costs included in the budget impact analysis

Treatment	Drug acquisition cost per patient per year	Administration cost per patient per year	Total cost per patient per year
Docetaxel	£162.20	£2,413.23	£2,575.43
Paclitaxel	£223.85	£2,413.23	£2,637.09
Methotrexate	£158.55	£2,413.23	£2,571.79
Nivolumab (without PAS)	[redacted]	£1,631.62	[redacted]
Nivolumab (with PAS)	[redacted]	£1,631.62	[redacted]

Based on per patient costs accrued in the first year of treatment in the cost-effectiveness analysis described in Section 5.2. Unit costs for drug acquisition and administration are presented in Section 5.5.2.

Abbreviations: PAS: Patient Access Scheme.

6.5 Unit costs

The unit costs included in the budget impact analysis are consistent with those used in the cost-effectiveness analysis, described in Section 5.5.

6.6 Estimates of resource savings

There are no estimates of resource savings although nivolumab is associated with fewer adverse events for patients versus the standard of care.

6.7 Estimated annual budget impact on the NHS in England and Wales

The budget impact analysis compares total costs over a 5-year time horizon between scenarios with and without nivolumab, with Year 1 coinciding with the introduction of nivolumab in the former scenario. The annual net budget impact associated with the introduction of nivolumab is presented in Table 84 (without PAS) and Table 85 (with PAS); by Year 5, the annual net budget impact of introducing nivolumab is estimated to be £[redacted] (with PAS).

Results of these analyses are limited by the accuracy of market share predictions. Furthermore, by only modelling a closed cohort, the analysis does not include patients who may continue to receive treatment across the 5-year time horizon.

Table 84: Estimated annual budget impact to NHS England and Wales of introducing nivolumab – over the first 5 years (without PAS for nivolumab)

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
NHS without nivolumab					
Docetaxel	£890,496	£890,496	£890,496	£890,496	£890,496
Paclitaxel	£303,938	£303,938	£303,938	£303,938	£303,938
Methotrexate	£296,412	£296,412	£296,412	£296,412	£296,412
Total cost	£1,490,846	£1,490,846	£1,490,846	£1,490,846	£1,490,846
NHS with nivolumab					
Docetaxel	£682,283	£474,071	£474,071	£474,071	£474,071
Paclitaxel	£232,873	£161,807	£161,807	£161,807	£161,807
Methotrexate	£227,106	£157,800	£157,800	£157,800	£157,800
Nivolumab (without PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative net budget impact					[redacted]

Abbreviations: NHS: National Health Service; PAS: Patient Access Scheme.

Table 85: Estimated annual budget impact to NHS England and Wales of introducing nivolumab – over the first 5 years (with PAS for nivolumab)

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
NHS without nivolumab					
Docetaxel	£890,496	£890,496	£890,496	£890,496	£890,496
Paclitaxel	£303,938	£303,938	£303,938	£303,938	£303,938
Methotrexate	£296,412	£296,412	£296,412	£296,412	£296,412
Total cost	£1,490,846	£1,490,846	£1,490,846	£1,490,846	£1,490,846
NHS with nivolumab					
Docetaxel	£682,283	£474,071	£474,071	£474,071	£474,071
Paclitaxel	£232,873	£161,807	£161,807	£161,807	£161,807
Methotrexate	£227,106	£157,800	£157,800	£157,800	£157,800
Nivolumab (with PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative net budget impact					[redacted]

Abbreviations: NHS: National Health Service; PAS: Patient Access Scheme.

7 References

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8 Appendices

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Single technology appraisal

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

Dear Sarah,

The Evidence Review Group, Kleijnen Systematic Reviews Ltd, and the technical team at NICE have looked at the submission received on 24 August 2016 from Bristol-Myers Squibb (BMS). In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **5 October 2016**.Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sana Khan, Technical Lead (Sana.Khan@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Literature searching

1. **Priority question**: The Evidence Review Group (ERG) notes considerable differences between the original clinical effectiveness Medline/Embase search in Embase.com (which is 48 lines long) and updated Medline/Embase search in Ovid (which is 109 lines long). A footnote to Table 1 in Appendix 1 of the company submission (CS) states that measures were taken to include additional synonyms in the Ovid translation of the original strategy.[1] Given the brevity of the original strategy, please clarify what measures were taken to ensure the original strategy was adequately comprehensive and comparable to the updated search strategy.

2. **Priority question**: Please clarify why the clinical effectiveness searches were updated in July 2016, but the cost-effectiveness searches were not. The cost-effectiveness searches were last conducted in September 2015. Please update the cost-effectiveness search to 2016, screen the results and provide any additional data.

3. Please provide the rationale for:
    a. limiting the combined Medline/Embase clinical effectiveness search to English language publications only.
    b. limiting the combined Medline/Embase cost effectiveness search to English language publications.
4. Please explain why the English language restriction was not applied to:
    a. the PubMed and Cochrane Library clinical effectiveness searches.
    b. the PubMed and Cochrane Library cost effectiveness searches.

5. Please clarify why the same limit to identify In-Process citations in PubMed was not applied to both the original and the updated clinical effectiveness PubMed search. The original search was limited with a different syntax [(pubstatusaheadofprint OR inprocess[sb])] to both the updated clinical effectiveness PubMed search and the cost effectiveness PubMed search [pubstatusaheadofprint]. Please explain this difference.

6. Please clarify how reports of adverse events (AEs) were identified. If separate AE searches were conducted, please report the full search methods and provide full search strategies for each resource searched in sufficient detail for the ERG to replicate the search.

7. Please provide URLs, date of search and search terms:
    a. used for the clinical effectiveness conference searching.
    b. used for the cost effectiveness conference searching.

8. Please explain why the cost effectiveness Medline/Embase and Cochrane Library searches were limited from 2005-2015.

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Section A: Clarification on effectiveness data

A1. **Priority question:** As cetuximab is not included in the final scope, please provide all analyses of nivolumab excluding the n=15 patients randomised to cetuximab.[2] This would include analyses of overall survival (OS), progression-free survival (PFS), time to treatment discontinuation (TTD) and adverse events (AEs). Alternatively, please provide the rationale as to why this has not been done.

A2. **Priority question:** The CheckMate 141 CSR provides OS hazard ratios (HRs) for nivolumab vs. each of the Investigator Choice (IC) therapies i.e. docetaxel, methotrexate and cetuximab (Figure 7.2-2).[3]

   a. Please provide HRs from an analysis stratified by prior cetuximab therapy as used in the primary analysis for a comparison of nivolumab vs. each of the comparators i.e. docetaxel, methotrexate and cetuximab, including 95% confidence intervals (CIs). Please also provide estimates of median survival from this stratified analysis with 95% CIs for each of the comparators i.e. docetaxel, methotrexate and cetuximab.

   b. Please also provide an analysis for a comparison of nivolumab vs. each of the comparators stratified by prior cetuximab therapy by selected baseline characteristics to estimate overall survival as in Figure 17 of the CS i.e. by intended IC.

A3. **Priority question:** Table 5 in Appendix 3 of the company submission (CS) contains a list of subsequent therapies in the CheckMate 141 trial.[1]

   a. Please state the rules that existed in the protocol for taking subsequent therapies.

   b. If no such rules existed, please explain how clinicians were instructed at any point as to whether to prescribe subsequent therapies, when to prescribe them and which ones.

   c. Please explain why many more patients in the nivolumab arm compared with the IC arm ([redacted] vs. [redacted] patients) received [redacted].

   d. Given that there might be an imbalance in the type or timing of subsequent therapy, the ERG kindly requests the following exploratory analyses of OS be presented:

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i. Simple censoring of any patient who has received subsequent systemic cancer therapy.

ii. Censoring using a method to control for informed censoring such as inverse probability of censoring weights (IPCW), as recommended in the NICE Decision Support Unit Technical Support Document 16.[4]

A4. In Figure 6 in the CS, it appears that patients are eligible for nivolumab at one of two places in the care pathway, after receiving platinum-based chemotherapy either pre- or post- progression to recurrent/metastatic (R/M) disease.[5]

a. Figure 58 appears to show that patients are only eligible after receipt of a first line of platinum-based therapy for R/M disease if progression occurs after 6 months (and not within 6 months). This figure appears to be based on the evidence of only one clinical expert.[6] It might be the case that patients who progress within 6 months are not able to receive platinum-based therapy because they are assumed to be resistant to all platinum-based therapy, but this is not explicitly stated. Please provide any further justification that patients are only eligible for nivolumab at 2nd line if progression to R/M disease occurs more than 6 months after first receiving platinum-based chemotherapy."

b. It appears from Figure 58 that patients who progress following platinum-based chemotherapy for R/M disease had to have received platinum-based chemoradiotherapy before progression to R/M disease i.e. 93% of those who receive any chemoradiotherapy. Please explain why patients who progress following platinum-based chemotherapy cannot be eligible for nivolumab if they have received non-platinum-based chemoradiotherapy.

A5. As stated in Table 9 in the CS, one of the inclusion criteria in the trial is the following: *'Tumour progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (i.e. with radiation after surgery), primary (i.e. with radiation), recurrent, or metastatic setting.'*[5] Please explain how this trial is applicable to the population defined in the scope, which does not exclude patients whose disease progress following receipt of platinum-based therapy after 6 months.

A6. According to the CS, p. 30, the ratio of males to females affected by SCCHN is 2.4:1, which would, assuming an equal mortality rate, imply a prevalence of approximately 70% male.[1] However, in the CheckMate 141 trial, 83.1% are male (Table 13 of the CS). In addition, the CheckMate 141 clinical study report (CSR) Figure 7.2.1-1 shows a large difference due to sex i.e., HR for overall survival (OS) of nivolumab versus individual investigator's choice therapies was 0.65 (95% (CI) 0.48, 0.88) for males and 0.93 (95% CI 0.47, 1.85) for female.[3]

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a. Please explain how the CheckMate 141 trial is representative of the SCCHN population given this apparent discrepancy"

A7. According to Figure 7.2.1-1 in the CSR, there is a large difference in the OS HRs between North America and the European Union (EU), i.e. 0.55 (95% CI 0.36, 0.85) and 0.91 (95% CI 0.62, 1.33) respectively.[3] Please explain this difference.

A8. The CheckMate 141 trial treated patients with docetaxel at a dose of 30 mg/m^2 every week, but, as stated in the CS, is prescribed every 3 weeks.[1] Indeed, the latest United Kingdom National Multidisciplinary Guidelines Head and Neck Cancer, p. S187, recommend a regimen of 75-100 mg/m^2 every 3 weeks.[7]

a. Please explain why the weekly regimen was chosen for the CheckMate 141 trial.

b. Please provide evidence as to the relative efficacy of weekly vs. 3 weekly administrations.

A9. Section 4.11 of the CS contains no evidence.[1] However, four non-controlled studies of paclitaxel were reported in Table 17 of the CS. Also, one randomised control trial (RCT) with paclitaxel as one of the arms was also reported in Table 17. Although, no indirect comparison is possible, it would be useful to see the results of these studies in order to help to validate the claim that there is no difference between paclitaxel and any of the therapies in the Investigator Choice arm of the CheckMate 141 trial.[3] Please provide a review of these five studies, including any results for OS and PFS.

A10. The CS states on p. 89 that *'The next database lock of the CheckMate 141 trial is expected in* [redacted] *from which updated efficacy analyses will be conducted.'*[1] Please confirm whether the results of these analyses are available now and if so consider updating the current analyses to include all available data.If data is not available at present, please provide a date when this is expected.

A11. In Section 5.2.4 on p.98 the CS states: *'The treatment of patients beyond disease progression is consistent with the trial protocol for CheckMate 141 (see Section 4.3), and the licensed posology for nivolumab which states that "treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient."'*[1]

a. Please provide the definition of 'clinical benefit' used in the trial.

b. Please verify whether this definition is in line with current UK clinical practice.

Section B: Clarification on cost-effectiveness data

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Treatment effectiveness

B1. **Priority:** the coefficients and parameterisations of the time-to-event models were not provided either in the CS or in the economic model.[5] Moreover, these parameters were not incorporated in the probabilistic sensitivity analysis (PSA).

a. Please provide the coefficients used to estimate OS, PFS and TTD in the model (for all different distributions), as well as the covariance matrix.

b. Please provide the formulas used to estimate OS, PFS and TTD in the model (for all different distributions).

c. Please incorporate the time-to-event models used to estimate OS, PFS and TTD in the model as probabilistic parameters in the probabilistic sensitivity analyses of the CS base-case and all requested analyses in this clarification letter.

d. Please provide an updated model including these amendments.

B2. **Priority:** In the CS, equivalent effectiveness of docetaxel and methotrexate is assumed.[5] However, the references provided by the company to justify this assumption indicated that methotrexate is marginally less effective than docetaxel (clinical expert opinion)[8] and that methotrexate has a statistically significant lower response than docetaxel (randomised phase II trial in patients with recurrent head and neck cancer).[9]

a. Please provide a revised version of section 5.3 of the CS (including OS, PFS, TTD and AEs) relaxing the assumption of equivalent effectiveness of docetaxel and methotrexate. More specifically use treatment specific effectiveness estimates for docetaxel and methotrexate, while using the matched 'intended investigator's choice' as a covariate for the nivolumab comparator. Please also provide the rationale as to why this analysis has not been done.

b. Please provide a scenario analysis using docetaxel as 'intended investigator's choice' for the nivolumab comparator and another scenario analysis using methotrexate as 'intended investigator's choice' for the nivolumab comparator.

c. Please provide an updated model including these estimates.

B3. **Priority:** In the CS, equivalent effectiveness of docetaxel and paclitaxel is assumed.[5] This assumption is justified in the CS by two references.[6, 10] However, the ERG could not find any trial evidence in these references to support the assumption of equivalent effectiveness of docetaxel and paclitaxel. Indeed, one

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reference seems to indicate that docetaxel is inferior to paclitaxel at least in combination with platinum-based therapies: 'Regimens with carboplatin and paclitaxel did not seem to be much different from regimens with cisplatin and paclitaxel. However, a recently reported phase II trial in R/M-SCCHN (including patients with Eastern Cooperative Oncology Group (ECOG) grade 0–2) conducted by the Southwest Oncology Group indicated only moderate activity of carboplatin plus docetaxel.' (p. vii254)

a. Please provide specific information from these references or other sources to justify the assumption of equivalent effectiveness of docetaxel and paclitaxel.

B4. For the time-to-event models for PFS and TTD, the company used generalised-gamma and log-logistic distributions respectively.

a. Please justify why the generalised-gamma distribution was used for PFS, because 1) the log-logistic distribution had a better statistical fit and 2) no plausible argument to deviate from this distribution was mentioned in the CS.[5] Note that the argument of visual inspection of fit with the Kaplan-Meier curve does not seem credible as this is inconsistent with the AIC/BIC.

b. Please justify why the log-logistic distribution was used for TTD and not the generalised-gamma distribution. The statement in CS section 5.3.4.1 regarding slightly better statistical fit for both nivolumab and IC is incorrect, as the generalised-gamma distribution provides the best statistical fit (according to the Akaike information criterion (AIC) in CS Table 34).

Adverse events

B5. The impact of AEs on health related quality of life and costs is incorporated only at the first cycle in the economic model.

a. Please provide a justification for this approach.

b. Please provide a scenario analysis incorporating the impact of AE on health related quality of life and costs over time.

c. Please provide an updated model including these estimates.

B6. CS Table 21 shows treatment-related 'select' AEs from the CheckMate 141 trial with a potential immunological cause that are of special clinical interest with the use of nivolumab. These AEs with a potential immunological cause were analysed according to organ category (skin, gastrointestinal, endocrine, pulmonary, hepatic, and renal).[5] but were not incorporated in the economic model.

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a. Please provide a cost-effectiveness scenario including treatment-related 'select' AEs reported in CS Table 21.

b. Please provide an updated model including these estimates.

Health related quality of life

B7. **Priority:** In the CS, the utility is estimated based on the CheckMate 141 trial using the EQ-5D-3L questionnaire.[5] However, data for both EQ-5D-3L and tumour response in [redacted] of 361 patients ([redacted]) were completely missing (i.e. unable to calculate a utility score at any time point).

a. Please compare patients characteristics of patients which were included and patients excluded from utility values calculations for both treatment groups separately and for the whole trial population combined (independent of treatment groups).

b. Please clarify what the likely causes of missing data were and what the potential impact of these missing data on the estimation of the utility scores would be, separately for patients who had completely and partially missing utility data.

c. Please recalculate the figures reported in CS Table 38 while imputing missing values (for the patients with completely missing utility data and patients with partially missing utility data) using multiple imputation (incorporating potential explanatory variables and using at least 10 imputations).

i. Please provide in detail, the methods used to impute and pool the utility data.

ii. Please provide a scenario analysis using these newly calculated utility values

iii. Please provide an updated model containing these updated utility values

d. Please provide the Table requested above (CS Table 38 while imputing missing values, question B6c) stratified for patients being on treatment (nivolumab or IC) or not.

e. Please provide the imputed utility values for every measurement occasion in the trial (including mean, number of observations, and standard deviation (SD)), stratified by treatment (nivolumab or IC), for:

i. Pre-progression

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ii. Post-progression

iii. On treatment (i.e. on nivolumab or IC)

iv. Off treatment (i.e. off nivolumab and IC)

f. Please provide the utility data requested above (question B7e) using the dataset without imputation.

g. Please justify why each EQ-5D-3L measurement was assumed to be independent while some patients had multiple EQ-5D-3L measurements and clarify what the expected impact of this method is on the results (i.e. why the company believes this would not bias the results).

Resource use and costs

B8. B8. In the CS, the proportion of patients receiving subsequent treatments is based on clinical trial data in the base case and thus assumed to be dependent on the initial treatment (see CS Table 46).[5]

a. Please justify why the proportion of patients receiving subsequent treatments is dependent on the initial treatment instead of being assumed to be equal for all comparators.

b. Please justify why the costs of subsequent treatments are assumed to be independent of the initial treatment, which is inconsistent with the differential proportion of patients receiving subsequent treatments. This is also inconsistent with the fact that many more patients in the nivolumab arm received 'experimental drugs'.

B9. Table 50 refers to previous technology appraisals (TAs) as source for the cost of different adverse events.[5]

a. Please provide full references to the primary sources used in the previous TAs and a digital copy of the primary sources.

Sensitivity and scenario analyses

B10. Please justify why a 15% variation around the mean has been implemented in the deterministic and probabilistic sensitivity analyses to calculate the confidence intervals and the SD respectively of several parameters.

a. Please perform deterministic sensitivity analyses on the parameters of OS, PFS and TTD (implementing parameter uncertainty using the response to question B1).

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b. Please provide the deterministic sensitivity analyses results while incorporating appropriate ranges i.e. use 95% CI based on evidence/empirical data whenever possible.

c. Please incorporate appropriate SD estimates in the probabilistic sensitivity analyses i.e. estimated based on evidence/empirical data whenever possible. For example, in case National Health Service reference costs are used, please use lower and upper quartiles in order to incorporate a suitable distribution in the PSA.

B11. Please provide a scenario analysis while estimating OS, PFS and TTD based on the EU region subgroup (subgroups as defined for Figures 7.2.1-1 and 7.3.1-1 in the CSR).[3]

Cost effectiveness results

B12. Please provide disaggregated life-years gained by health states for nivolumab and all comparators (as provided for quality adjusted life-years gained in Table 56 of the CS).[5]

B13. Please provide an updated model which allows for probabilistic analyses of multiple treatments simultaneously.

Section C: Textual clarifications and additional points

None.

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References

1. Bristol-Myers Squibb Pharmaceuticals Ltd. Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]. Company evidence submission: appendices. Single technology appraisal (STA). August 2016.
2. National Institute for Health and Care Excellence. Single Technology Appraisal. Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy: Final scope (Appendix B) [Internet]. 2016 [accessed 7.9.16].
3. Bristol-Myers Squibb. An open label, randomized phase 3 clinical trial of nivolumab vs therapy of investigator's choice in recurrent or metastatic platinum squamous cell carcinoma of the head and neck (SCCHN): Final Clinical Study Report for Study CA209141. Document Control Number: 930102367 (CHECKMATE 141) [PDF provided with the company's submission]. Lawrenceville, US: Bristol-Myers Squibb2016 [accessed 8.9.16].
4. Latimer N, Abrams K. NICE DSU Technical Support Document 16: adjusting survival time estimates in the presence of treatment switching [Internet]2014 [accessed 14.9.16].
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8. Bristol-Myers Squibb. Clinical workshop to support the development of health economic models for nivolumab in squamous cell carcinoma of the head and neck: meeting minutes (3rd June 2016) [Word document provided with the company's submission]: Bristol-Myers Squibb2016 [accessed 13.9.16].
9. Guardiola E, Peyrade F, Chaigneau L, Cupissol D, Tchiknavorian X, Bompas E, et al. Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. Eur J Cancer. 2004;40(14):2071–6.
10. Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. Ann Oncol. 2010;21 Suppl 7:vii252-61. doi:mdq453 [pii] 10.1093/annonc/mdq453 [doi].

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Single technology appraisal

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

Dear Helen Knight,

Thank you for the opportunity to respond to the clarification questions from the Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE. We thank the team for their general comments on the submission and hope that our responses to the individual questions in turn below provide clarity for our approach in the submission and the necessary additional information where this has been possible.

As requested, we have uploaded to NICE Docs two versions of this response letter: one with academic/commercial-in-confidence information clearly marked and one with this information removed. In addition, we have uploaded two versions of the economic model. The purpose of these two models is explained in the context of our responses to the questions below.

Please do not hesitate to get in touch should you have any questions regarding our response.

Kind regards,

Sarah Breen

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Literature searching

1. **Priority question**: The Evidence Review Group (ERG) notes considerable differences between the original clinical effectiveness Medline/Embase search in Embase.com (which is 48 lines long) and updated Medline/Embase search in Ovid (which is 109 lines long). A footnote to Table 1 in Appendix 1 of the company submission (CS) states that measures were taken to include additional synonyms in the Ovid translation of the original strategy.[1] Given the brevity of the original strategy, please clarify what measures were taken to ensure the original strategy was adequately comprehensive and comparable to the updated search strategy.

The original search strategy was run on Embase.com using "/syn" and "/exp" functions. The difference in approach in the two search strategies was needed as a result of there being no equivalent syntax for the '/syn' terms searched in Embase.com for the original review in Ovid SP, the platform used in the updated review.

The '/syn' syntax in Embase.com is equivalent to searching for all Emtree thesaurus synonyms for that term in addition to any 'narrower' Emtree terms. In order to try to replicate this in Ovid, we manually looked up the thesaurus synonyms and narrower Emtree terms and added these as .mp,sh and subject heading terms, respectively to the Ovid strategy. Therefore, the synonyms searched in the updated searches were intended to represent the same terms searched in the original review, rather than additional terms.

A few examples of the use of the synonyms and narrower terms can be seen in Table 1 below.

Table 1: Examples of synonyms and narrower terms used in the original and updated reviews

Original review	Updated review
'nivolumab'/syn Synonyms covered by "/syn" function include nivolumab; bms 936558; bms936558; mdx 1106; mdx1106; ono 4538; ono4538; opdivo *No narrower terms were covered by the /syn function*	(nivolumab or "bms 936558" or bms936558 or "mdx 1106" or mdx1106 or "ono 4538" or ono4538 or opdivo).mp,sh.
'Head and neck cancer'/syn Synonyms covered by /syn function include head and neck cancer; cancer, head and neck; cervicofacial cancer; ear nose throat cancer; ENT cancer; head neck cancer; ORL cancer; otorhinolaryngeal cancer; otorhinolaryngologic cancer; otorhinolaryngological cancer	("head and neck cancer" or "cancer, head and neck" or "cervicofacial cancer" or "ear nose throat cancer" or "ENT cancer" or "head neck cancer" or "ORL cancer" or "otorhinolaryngeal cancer" or "otorhinolaryngologic cancer" or "otorhinolaryngological cancer").mp,sh. or

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Narrower terms covered by /syn function include eye cancer; face cancer; head and neck carcinoma; head and neck squamous cell carcinoma; head cancer; jaw cancer; lip cancer; mouth cancer; neck cancer; nose cancer; orbit cancer; paranasal sinus cancer; pharynx cancer; salivary gland cancer; tongue cancer; tonsil cancer	"head and neck cancer"/ or eye cancer/ or face cancer/ or "head and neck carcinoma"/ or "head and neck squamous cell carcinoma"/ or head cancer/ or jaw cancer/ or lip cancer/ or mouth cancer/ or neck cancer/ or nose cancer/ or orbit cancer/ or paranasal sinus cancer/ or pharynx cancer/ or salivary gland cancer/ or tongue cancer/ or tonsil cancer/
Laryngectomy/syn Synonyms covered by /syn function include laryngectomy; laryngectomized subject; partial laryngectomy *No narrower terms were covered by the /syn function*	(laryngectomy or "laryngectomized subject" or "partial laryngectomy").mp,sh.

This approach has further been specified in the table footnote of Table 1 in Appendix 1 of the CS, which states that 'Terms searched as /syn in Embase.com do not have a direct equivalent in Ovid, and have therefore been translated as the term plus any synonyms identified through the Ovid Thesaurus searched as .mp,sh (abstract, device manufacturer, device trade name, drug manufacturer, drug trade name, heading word, keyword, keyword heading word, name of substance word, original title, title, unique identifier, subject headings). Additionally, subject headings for related 'narrower terms' identified via the Ovid Thesaurus have also been searched in these cases.'

In the original search strategy (see Table 1 in Appendix 1 of the CS), the intervention term group lists all the interventions searched using "/syn" function in single row (Row 42), while in the updated search strategy each intervention has been searched separately along with its associated synonyms which are otherwise naturally retrieved using "/syn" function in the original search strategy. Thus, Row 60 to Row 100 in the updated search strategy covers interventions and the synonyms corresponding to Row 42 of the original search strategy with no differences.

Further, the search strategy used in the original review was validated against existing systematic reviews to ensure that all the relevant clinical trials included in the previous reviews were captured in the current strategy as well. The search strategy was validated against recently conducted systematic reviews including Vermorken 2010 and Suh 2014. All the studies relevant to the review objective could be mapped to those identified by the previously published reviews.

Thus, the search strategy used in the original review is a reproducible, validated, and comprehensive search strategy.

2. **Priority question**: Please clarify why the clinical effectiveness searches were updated in July 2016, but the cost-effectiveness searches were not. The cost-

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effectiveness searches were last conducted in September 2015. Please update the cost-effectiveness search to 2016, screen the results and provide any additional data.

Following this request, an update to the economic systematic literature review (SLR) has been performed. This update adhered to the same methodology as described for the original search of cost effectiveness studies in Section 5.1 of our submission. The databases searched in the update review were Embase® and PubMed® (covering MEDLINE® and MEDLINE In-Process®). The conferences listed in Table 2 were additionally searched on 29th September 2016.

Table 2: List of conferences searched for update to cost-effectiveness search

Conference	Link
American Head and Neck Society (AHNS)	http://ahns.jnabstracts.com/
American Society of Clinical Oncology (ASCO 2016)	http://meeting.ascopubs.org/search?tocsectionid=Head+and+Neck+Cancer&displaysectionid=Head+and+Neck+Cancer&volume=34&issue=15_suppl&hits=10&submit=Submit
American Society of Clinical Oncology- Quality of care Symposium (ASCO 2016)	http://meeting.ascopubs.org/content/vol34/7_suppl

The database searches retrieved a total of 823 hits, of which 4 trials met the eligibility criteria of the review as described in Section 5.1 (Table 23) of our original submission. A further one conference abstract of relevance to the review criteria was identified from the conference proceedings of American Head and Neck Society (AHNS) 2016. A list of these five studies is provided in Table 3.

Table 3: Summary of the five studies identified in the update

Author	Study reference	Country
Rowan 2016	Utility of a perioperative nutritional intervention on postoperative outcomes in high-risk head & neck cancer patients. Oral Oncology. 2016; 42(46):54	USA
White 2016	Heroic head and neck cancer surgery, costs and complications. AHNS 2016. SO97.	NR
Baxi 2016	Patients with Recurrent/Metastatic Head and Neck Cancer: Understanding the Burden of Disease. Value in Health. 2016; 19(3):A168	USA
Divi 2016	Geographic variation in Medicare treatment costs and outcomes for advanced head and neck cancer. Oral Oncology. 2016; 61:83	USA
Lanni 2015	Development of a weekly nutrition clinic for head and neck cancer patients: Does it make a difference? Oncology Biology Physics. 2016; 93(3):E488	USA

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None of the identified studies presented economic evaluations that evaluated the cost-effectiveness of nivolumab or included patients with R/M SCCHN who had progressed after platinum-based therapy. Instead, all identified studies reported cost or resource use data only but none were conducted in the UK. As such, no additional data were identified in the systematic review update that were considered relevant (i.e., from a UK NHS/PSS perspective) for inclusion in the *de novo* cost-effectiveness analysis.

3. Please provide the rationale for:
    a. limiting the combined Medline/Embase clinical effectiveness search to English language publications only.
    b. limiting the combined Medline/Embase cost effectiveness search to English language publications.

Data pertaining to clinical and cost-effectiveness for SCCHN were identified by the searches when restricting to English language publications only. According to the Cochrane Handbook for Systematic Reviews of Interventions, the potential impact of studies published in languages other than English in a meta-analysis may be minimal because of the shift towards publication of studies in English. This is further supported by a comprehensive study by Morrison et al., which found no evidence of a systematic bias from the use of language restrictions in systematic review-based meta-analyses in conventional medicine. Further, the handbook states that review authors may want to search without language restrictions but if they do so then decisions about including reports from languages other than English may need to be taken on a case-by-case basis. Finally, systematic literature reviews for clinical and cost-effectiveness evidence that have been performed for previous NICE appraisals have frequently excluded non-English language publications from their search terms of eligibility criteria. As such, given that clinical and cost-effectiveness evidence had been identified by the searches when restricting to the English language, a pragmatic decision to not expand the search to non-English language articles was made.

4. Please explain why the English language restriction was not applied to:
    a. the PubMed and Cochrane Library clinical effectiveness searches.
    b. the PubMed and Cochrane Library cost effectiveness searches.

For both the searches conducted in the Cochrane Library and in PubMed, records published in languages other than English were manually excluded at the data collection stage rather than the search term stage. However, the English language restriction was applied in the review.

5. Please clarify why the same limit to identify In-Process citations in PubMed was not applied to both the original and the updated clinical effectiveness PubMed search. The original search was limited with a different syntax [(pubstatusaheadofprint OR inprocess[sb])] to both the updated clinical effectiveness PubMed search and the cost effectiveness PubMed search [pubstatusaheadofprint]. Please explain this difference.

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The 'inprocess[sb]' term is used in PubMed to identify citations that are under review for inclusion in MEDLINE. In the updated clinical effectiveness review, these articles were identified via the Ovid SP searches (MEDLINE In-Process database), therefore this search term was redundant in the updated PubMed search.

6. Please clarify how reports of adverse events (AEs) were identified. If separate AE searches were conducted, please report the full search methods and provide full search strategies for each resource searched in sufficient detail for the ERG to replicate the search.

Both the original and the updated searches included terms for various interventions evaluated in SCCHN and were not limited by the type of outcome evaluated or data reported. Evidence was retrieved irrespective of whether efficacy or safety data were reported. Further, no exclusions were made at the data collection stage based on the type of outcome evaluated/reported across publications. Studies evaluating either efficacy or safety data or both were retrieved by the searches and thus evaluated for inclusion in to the review, hence no separate searches for adverse event reports were conducted.

7. Please provide URLs, date of search and search terms:
    a. used for the clinical effectiveness conference searching.
    b. used for the cost effectiveness conference searching.

The URLs of the conferences searched in both the original and the updated clinical effectiveness and cost-effectiveness reviews are provided in Table 4 below. The original searches were conducted in December 2015. In the clinical review update, only the American Society of Clinical Oncology 2016 conference was searched, since the other 2016 conferences had not taken place at the time the review update was conducted. This search took place in June 2016.

During the conference searching, only the abstracts under relevant headings from the conference proceedings were searched. Use of keywords was avoided due to variable reporting of disease across the studies for example SCCHN, HNSCC, head and neck, oral, pharynx, pharyngeal, etc. So, in order to avoid missing any relevant study, all the abstracts published in conference proceedings were screened for inclusion.

Table 4: List of conferences searched in December 2015 for the clinical and cost effectiveness reviews

Conference	Year	Hyperlink	Search terms
Conferences searched for both the clinical effectiveness and the cost-effectiveness reviews			
American Society of Clinical Oncology (ASCO)	2013	http://meetinglibrary.asco.org/abstractbysubcategory/2013%20ASCO%20Annual%20Meeting/108	The searches for identification

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Conference	Year	Hyperlink	Search terms
American Society of Clinical Oncology (ASCO)	2014	http://meetinglibrary.asco.org/abstractbysubcategory/2014%20ASCO%20Annual%20Meeting/108	of relevant abstracts published in the conferences proceedings were not restricted by any particular keywords.
American Society of Clinical Oncology (ASCO)	2015	http://meetinglibrary.asco.org/abstractbysubcategory/2015%20ASCO%20Annual%20Meeting/108	
American Society of Clinical Oncology (ASCO)	2016	http://meetinglibrary.asco.org/subcategories/2016%20ASCO%20Annual%20Meeting	
European Society for Medical Oncology (ESMO)	2013	http://annonc.oxfordjournals.org/content/by/year/2013	
European Society for Medical Oncology (ESMO)	2014	http://annonc.oxfordjournals.org/content/by/year/2014	
European Society for Medical Oncology (ESMO)	2015	http://www.europeancancercongress.org/Scientific-Programme/Searchable-Programme#anchorScpr	
American Head and Neck society (AHNS)	2013	http://ahns.jnabstracts.com/2013/	
American Head and Neck society (AHNS)	2014	http://ahns.jnabstracts.com/2014/	
American Head and Neck society (AHNS)	2015	http://ahns.jnabstracts.com/	
Conferences searched for the cost-effectiveness review			
International Society of Pharmacoeconomics and Outcomes Research (ISPOR)	2013	http://www.ispor.org/publications/value/JVAL_16-3_FINAL.pdf	The searches for identification of relevant abstracts published in the conferences proceedings were not restricted by any particular keywords.
International Society of Pharmacoeconomics and Outcomes Research (ISPOR)	2014	http://www.ispor.org/publications/value/VIH_17-3_final.pdf	
International Society of Pharmacoeconomics and Outcomes Research (ISPOR)	2015	http://www.valueinhealthjournal.com/issue/S1098-3015(14)X0011-2	
ISPOR Annual European Congress	2013	http://www.ispor.org/publications/value/jval_16-7_final.pdf	
ISPOR Annual European Congress	2014	http://www.valueinhealthjournal.com/issue/S1098-3015(14)X0007-0	
ISPOR Annual European Congress	2015	http://www.valueinhealthjournal.com/issue/S1098-3015(14)X0015-X	
American Society of Clinical Oncology Quality Care Symposium (ASCO-QoC)	2013	http://meeting.ascopubs.org/content/vol31/31_suppl	

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Conference	Year	Hyperlink	Search terms
American Society of Clinical Oncology Quality Care Symposium (ASCO-QoC)	2014	http://meeting.ascopubs.org/content/vol32/30_suppl	
American Society of Clinical Oncology Quality Care Symposium (ASCO-QoC)	2015	*Symposium not held in 2015*	
Academy of Managed Care Pharmacy (AMCP)	2013	http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=16216	
Academy of Managed Care Pharmacy (AMCP)	2014	http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=17840	
Academy of Managed Care Pharmacy (AMCP)	2015	http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=19292	

8. Please explain why the cost effectiveness Medline/Embase and Cochrane Library searches were limited from 2005-2015.

The cost effectiveness review was restricted to the last ten years i.e. 2005 to 2015 to obtain the most recent evidence pertaining to the economic data for SCCHN.

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Section A: Clarification on effectiveness data

A1. **Priority question:** As cetuximab is not included in the final scope, please provide all analyses of nivolumab excluding the n=15 patients randomised to cetuximab. This would include analyses of overall survival (OS), progression-free survival (PFS), time to treatment discontinuation (TTD) and adverse events (AEs). Alternatively, please provide the rationale as to why this has not been done.

In the CS, clinical effectiveness results and safety data were presented from the all-randomised (intention to treat, ITT) and all-treated populations, respectively. As such, analyses were presented for nivolumab versus all patients in the IC arm, including those randomised to/treated with cetuximab.

The rationale for taking this approach in the original submission was detailed in Section 4.4 of the CS and is reproduced below:

"The sample size calculations that informed the CheckMate 141 trial design were conducted to ensure that the trial was sufficiently powered to detect differences in OS between treatment arms (nivolumab versus IC of therapy). The trial was therefore not designed to detect differences between nivolumab and the individual therapies that comprise the IC arm. The sample size for each individual therapy was relatively small in the IC arm, with 52, 46 and 13 patients, respectively, receiving at least one dose of docetaxel, methotrexate or cetuximab. Moreover, randomisation procedures did not hold in the assignment of patients to each of the three individual therapies comprising the IC arm, with the choice of intended IC therapy made at the investigator's discretion prior to randomisation. Thus, analysis of outcomes by therapies in the IC arm may be at risk for selection bias for observable and unobservable patient characteristics. Consequently, the main clinical effectiveness results presented in this submission are for comparisons between nivolumab and the IC arm as a whole."

In summary, by excluding patients who were randomised to IC and were intended to receive cetuximab the randomisation of patients to each treatment arm (nivolumab and IC) would have been broken. It should also be noted that the presentation of data from the ITT population is consistent with approach preferred in the NICE Single technology appraisal: user guide for company evidence submission template [PMG24], for Section 4.7:

"Data from intention‑to‑treat analyses should be presented whenever possible and a definition of the included participants provided."[2]

Finally, as the number of patients who were randomised to IC and were intended to receive cetuximab was relatively small (n=15), the inclusion of these patients (despite cetuximab not being included in the final scope) was not believed to have a major impact on the results from the ITT analysis. In response to the clarification question, the Kaplan-Meier plots for the analyses in which patients who were randomised to IC and were intended to receive cetuximab are excluded are presented in full in Figure 1 for OS, Figure 2 for PFS and Figure 3 for TTD. As can be seen in

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Table 5, the exclusion of patients who were randomised to IC and were intended to receive cetuximab has little effect on the results from the ITT analysis.

Table 5: OS, PFS and TTD results for investigator's choice (ITT and excluding cetuximab)

Outcome	Investigator's choice arm	
	ITT (n=121)	Excluding cetuximab (n=[redacted])
Median OS, months (95% CI)	5.1 (4.0, 6.0)	[redacted]
HR for death with nivolumab (97.73% CI; p-value)	0.70 (0.51, 0.96; p=0.03236)	[redacted]
Median PFS, months (95% CI)	2.3 (1.9, 3.1)	[redacted]
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)	[redacted]
Median TTD, months (95% CI)	1.9 (1.6, 2.0)	[redacted]

HR computed using stratified Cox proportional hazards model and p-value from stratified log-rank test, with prior cetuximab (yes/no IVRS source) as a stratification factor.

Abbreviations: CI: confidence intervals; HR: hazard ratio; ITT: intention to treat; IVRS: interactive voice response system; OS: overall survival; PFS: progression-free survival; TTD: time to discontinuation.

The type of AEs requested for this analysis has not been specified and as such safety data from the all-treated populations for nivolumab (n=236) and IC excluding cetuximab patients (n=98) are also presented in the accompanying document (Supplementary 1, commercial in confidence) for all-cause AEs (any grade, Grade 3–4, Grade 5) with incidence ≥10% in either treatment arm, all-cause AEs (any grade, Grade 3–4, Grade 5) leading to discontinuation, and drug-related AEs (any grade, Grade 3–4, Grade 5).

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Figure 1: Kaplan-Meier plot for overall survival in the all-randomised population, excluding cetuximab patients in the investigator's choice arm

Symbols represent censored observations
The boundary for statistical significance requires the p-value to be less than 0.0227
Hazard ratio computed using stratified Cox proportional hazards model and p-value from stratified log-rank test
With prior Cetuximab (yes/no IVRS source) as a stratification factor
Hazard Ratio of Nivolumab to Investigators Choice

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Figure 2: Kaplan-Meier plot for progression-free survival in the all-randomised population, excluding cetuximab patients in the investigator's choice arm

Symbols represent censored observations
Hazard ratio computed using stratified Cox proportional hazards model and p-value from stratified log-rank test with prior cetuximab (yes/no IVRS source) as a stratification factor
Hazard Ratio of Nivolumab to Investigators Choice

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Figure 3: Kaplan-Meier plot of duration of therapy in the all-treated population, excluding cetuximab patients in the investigator's choice arm

Symbols represent censored observations

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A2. **Priority question:** The CheckMate 141 CSR provides OS hazard ratios (HRs) for nivolumab vs. each of the Investigator Choice (IC) therapies i.e. docetaxel, methotrexate and cetuximab (Figure 7.2-2).

a. Please provide HRs from an analysis stratified by prior cetuximab therapy as used in the primary analysis for a comparison of nivolumab vs. each of the comparators i.e. docetaxel, methotrexate and cetuximab, including 95% confidence intervals (CIs). Please also provide estimates of median survival from this stratified analysis with 95% CIs for each of the comparators i.e. docetaxel, methotrexate and cetuximab.

In response to both Questions A2a and A2b, it should be noted that stratification by prior cetuximab therapy was conducted at randomisation into the two treatment arms (nivolumab and IC). As such, patients were not stratified by prior cetuximab within the IC arm, with intended choice of IC therapy having been designated by investigators prior to randomisation. For this reason, the subgroup analysis presented in the CheckMate CSR (Figure 7.2-2) was unstratified and is considered to be the most appropriate approach.[3]

For completeness, however, the Kaplan-Meier plot and HRs (stratified by prior cetuximab therapy) for the analyses of nivolumab versus each of the individual intended therapies in the IC arm are presented in Figure 4. These HRs are similar to those unstratified HRs presented in Figure 7.2-2 of the CSR ([redacted], and [redacted] for nivolumab versus methotrexate, docetaxel and cetuximab, respectively).[3] Median OS for each subgroup was not affected by stratifying for prior cetuximab therapy (shown in Figure 4 below).

Finally, as noted in the response to Question A1, the presentation of data by each individual intended therapy in the IC arm was not considered to be appropriate in the CS, given the reasons described above (i.e. small sample sizes, lack of statistical power, breaking of randomisation and potential unobservable or observable selection bias). As such, it is advised that caution should be taken when interpreting the results of subgroup analyses by intended therapy for the IC arm (applicable to results presented in response to both Questions A2a and A2b).

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Figure 4: Kaplan-Meier plots of overall survival by agent (nivolumab, cetuximab, methotrexate or docetaxel) in the all-randomised population, with hazard ratios stratified by prior cetuximab therapy

Symbols represent censored observations
Hazard ratio computed using stratified Cox proportional hazards model with prior cetuximab (yes/no IVRS source) as a stratification factor

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b. Please also provide an analysis for a comparison of nivolumab vs. each of the comparators stratified by prior cetuximab therapy by selected baseline characteristics to estimate overall survival as in Figure 17 of the CS i.e. by intended IC.

Analyses of OS for nivolumab versus each of the individual therapies in the IC arm stratified by prior cetuximab therapy, by selected baselines characteristics (age, <65 or ≥65 and <75 or ≥75; ECOG performance status, 0 or ≥1; tobacco use, current/former or never; and number of prior lines of therapy, 1 or 2 or ≥3) are presented in as forest plots in Figure 5 for cetuximab, Figure 6 for docetaxel and Figure 7 for methotrexate.

The interpretation of these results should take into account the caveats noted in the response to A2a, namely, that patients were not stratified by prior cetuximab therapy within the IC arm and that subgroup analyses by individual therapy in the IC arm are associated with small sample sizes, a break in randomisation, and may be subject to observable and unobservable selection bias. Given the further subgrouping of patients by both baseline characteristics and the individual therapy in the IC arm, these analyses are based on increasingly smaller sample sizes (see 'n' numbers provided in the below figures).

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Figure 5: Forest plot of treatment effect on overall survival in pre-defined subset – all-randomised patients to nivolumab and cetuximab

HR is not computed for subsets with 20 or fewer subjects in total (across treatment groups)
Hazard ratio computed using stratified Cox proportional hazards model with prior Cetuximab (yes/no IVRS source) as a stratification factor for nivolumab matched pairs used by intended IC therapy

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Figure 6: Forest plot of treatment effect on overall survival in pre-defined subset – all-randomised patients to nivolumab and docetaxel

HR is not computed for subsets with 20 or fewer subjects in total (across treatment groups)
Hazard ratio computed using stratified Cox proportional hazards model with prior Cetuximab (yes/no IVRS source) as a stratification factor for nivolumab matched pairs used by intended IC therapy

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Figure 7: Forest plot of treatment effect on overall survival in pre-defined subset – all-randomised patients to nivolumab and methotrexate

HR is not computed for subsets with 20 or fewer subjects in total (across treatment groups)
Hazard ratio computed using stratified Cox proportional hazards model with prior Cetuximab (yes/no IVRS source) as a stratification factor for nivolumab matched pairs used by intended IC therapy

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A3. **Priority question:** Table 5 in Appendix 3 of the company submission (CS) contains a list of subsequent therapies in the CheckMate 141 trial.[1]

a. Please state the rules that existed in the protocol for taking subsequent therapies.

The CheckMate 141 protocol did not give guidance to investigators on choice of subsequent therapies.

b. If no such rules existed, please explain how clinicians were instructed at any point as to whether to prescribe subsequent therapies, when to prescribe them and which ones.

The decision to stop therapy or to place the study participant on another subsequent therapy was based on whether the study participant had progressed on study or was unable to continue with the assigned therapy due to toxicity. BMS captured the type of subsequent therapy, but not the duration or response to the subsequent therapy chosen by the treating clinician.

c. Please explain why many more patients in the nivolumab arm compared with the IC arm (14 vs. 2 patients) received 'experimental drugs' e.g. ABBY 221.

Correction: It should be noted that the values stated in this question above have been incorrectly quoted from the CS. The number of patients receiving subsequent therapy with 'experimental drugs' in the nivolumab arm was 9 (not 14) versus 2 patients in the IC arm.[3] As patients were randomised 2:1, the difference in the proportions between the two treatment arms was (9/240) 3.75% for nivolumab versus (2/121) 1.65% for IC.

In addition, it should be noted that more patients in the IC arm received 'immunotherapy' as a subsequent therapy compared with those in the nivolumab arm (9 versus 5), of which pembrolizumab was received by 8 patients in the IC arm compared with 1 patient in the nivolumab arm.[3] Immunotherapy agents such as pembrolizumab and urelumab were also investigational agents at the time of conducting the CheckMate-141 trial and their separate categorisation as 'immunotherapy' is presumed to be for clinical relevance. In total, although more patients in the nivolumab arm were switched onto 'experimental drugs,' a higher proportion of patients in the IC arm received subsequent therapy with either an 'experimental drug' or investigational 'immunotherapy' agent (11/121, 9.1%), compared to nivolumab (18/240, 7.5%).[3]

CiC highlighting: Please note that data included in the question are taken from the CSR and are not expected to be published soon; these should therefore be marked as commercial in confidence. This marking has been added to the question in this response document.

d. Given that there might be an imbalance in the type or timing of subsequent therapy, the ERG kindly requests the following exploratory analyses of OS be presented:

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i. Simple censoring of any patient who has received subsequent systemic cancer therapy.

The proportion of patients receiving subsequent systemic therapy in CheckMate 141 was 35% in the nivolumab arm versus 38% in the IC arm. Moreover, the proportion of patients receiving subsequent systemic therapy was 29.6% versus 32.2% for nivolumab versus IC, respectively, and 7.5% versus 9.1% for patients receiving investigational therapies ('experimental drugs' and 'immunotherapies'). BMS does not therefore consider that there was an imbalance in the type of subsequent therapy received by patients in CheckMate 141, and especially not one that would favour nivolumab-treated patients.

Information regarding the timing of subsequent therapy was not collected as part of the trial. The timing of subsequent therapy would however depend on whether the study participant had progressed on study or was unable to continue with the assigned therapy due to toxicity – as noted in the CS, the median duration on initial therapy was similar between the two treatment arms in CheckMate 141 (both 1.9 months). As such, it is not believed that major imbalances in the timing of subsequent therapies would be expected.

In response to the request above, an analysis of OS using a simple censoring of patients that received subsequent systemic cancer therapy is presented in Figure 8. It should be noted that the HR of death for nivolumab versus IC in this analysis ([redacted]) is very similar to that observed in the primary analysis of OS (0.70; 0.51, 0.96), suggesting that the treatment effect of nivolumab versus IC is not affected by the type or timing of subsequent systemic therapy received in each treatment arm.

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Figure 8: Kaplan-Meier plot of overall survival, with censoring of patients who received subsequent systemic therapy

Symbols represent censored observations
Hazard ratio computed using stratified Cox proportional hazards model and p-value from stratified log-rank test with prior Cetuximab (yes/no IVRS source) as a stratification factor
Hazard Ratio of Nivolumab to Investigators Choice

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ii. Censoring using a method to control for informed censoring such as inverse probability of censoring weights (IPCW), as recommended in the NICE Decision Support Unit Technical Support Document 16.

As detailed above, BMS does not consider there to be an imbalance in the type of subsequent therapy between the two treatment arms. Additionally, it would not be possible, in the time permitted to respond to these clarification questions, to conduct an analysis controlling for informed censoring using the IPCW or other methods. Such methods are involved and require careful consideration of the underlying data in order to ensure that they are being used appropriately and provide meaningful and robust results.

A4. In Figure 6 in the CS, it appears that patients are eligible for nivolumab at one of two places in the care pathway, after receiving platinum-based chemotherapy either pre- or post- progression to recurrent/metastatic (R/M) disease.[1]

a. Figure 58 appears to show that patients are only eligible after receipt of a first line of platinum-based therapy for R/M disease if progression occurs after 6 months (and not within 6 months). This figure appears to be based on the evidence of only one clinical expert. It might be the case that patients who progress within 6 months are not able to receive platinum-based therapy because they are assumed to be resistant to all platinum-based therapy, but this is not explicitly stated. Please provide any further justification that patients are only eligible for nivolumab at 2nd line if progression to R/M disease occurs more than 6 months after first receiving platinum-based chemotherapy."

We acknowledge that some assumptions regarding the eligible patient population for nivolumab may have not been explicitly stated in the CS. To clarify, it is correct that patients are eligible for nivolumab at two places in the care pathway:

1. At first-line in R/M disease if they have progressed within 6 months of platinum-therapy at the locally-advanced stage
2. At second-line in R/M disease if they have:
    - Been diagnosed at the metastatic stage and received first-line platinum-based therapy in this stage
    - Progressed after 6 months of platinum-based therapy at the locally-advanced stage and then been re-treated with platinum-based therapy at first-line for R/M disease

It is correct that the assumption was made that patients who progress within 6 months of platinum-based therapy for locally-advanced disease are assumed to be platinum-refractory, and would therefore not receive platinum-based therapy in first-line in R/M disease. These patients would be eligible for nivolumab in first-line in R/M disease, since they have received prior platinum-based therapy in the locally-advanced setting.

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b. It appears from Figure 58 that patients who progress following platinum-based chemotherapy for R/M disease had to have received platinum-based chemoradiotherapy before progression to R/M disease i.e. 93% of those who receive any chemoradiotherapy. Please explain why patients who progress following platinum-based chemotherapy cannot be eligible for nivolumab if they have received non-platinum-based chemoradiotherapy.

As noted in the CS, the anticipated licence for nivolumab in SCCHN is as: "*a treatment of R/M SCCHN after platinum-based therapy in adults*." In clinical practice, patients would be expected to have progressed after receiving platinum-based therapy before they then received nivolumab (or another systemic anti-cancer therapy).

The vast majority (93%) of patients diagnosed with locally-advanced SCCHN who are treated are expected to receive platinum-based chemoradiotherapy in the locally-advanced setting. It was assumed that the 7% of patients who were not eligible for platinum-based chemoradiotherapy in the locally-advanced setting would either a) be unable to tolerate (i.e. contra-indicated) platinum-based therapy, b) not be fit enough to receive platinum-based therapy, or c) simply not wish to receive platinum-based chemoradiotherapy. This is a patient population for which treatment with cetuximab in combination with radiotherapy (as recommended by NICE TA145),[4] relates to. Given that these patients are platinum-ineligible in the locally-advanced setting it is very unlikely that they would go on to receive platinum-based chemotherapy at later stages of disease (i.e. in R/M disease).

In conclusion, this subset relates to only a very small number of patients (~78 patients) and it is assumed that these patients would not receive platinum-based therapy in the R/M setting if they were not considered appropriate candidates in the locally-advanced setting, where platinum-based chemoradiotherapy is the current standard of care.

A5. As stated in Table 9 in the CS, one of the inclusion criteria in the trial is the following: *'Tumour progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (i.e. with radiation after surgery), primary (i.e. with radiation), recurrent, or metastatic setting.'*[1] Please explain how this trial is applicable to the population defined in the scope, which does not exclude patients whose disease progress following receipt of platinum-based therapy after 6 months.

As noted in the CS, the anticipated licence for nivolumab in SCCHN is as: "*a treatment of R/M SCCHN after platinum-based therapy in adults*." In clinical practice, patients would be expected to have progressed after receiving platinum-based therapy before they then received nivolumab (or another systemic anti-cancer therapy). Additionally, it is likely that patients who have progressed after 6 months of receiving platinum-based therapy may then be re-treated with platinum-based therapy prior to receiving further systemic anti-cancer therapy.

By stipulating in the inclusion criteria that patients must have progressed within 6 months of the last dose of platinum-based therapy, the CheckMate 141 trial included those patients for whom platinum-based therapy was no longer an option – i.e., patients with R/M SCCHN *after* platinum-based therapy. The trial population is therefore consistent with the expected marketing

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authorisation for nivolumab and the scope for this appraisal and reflects the patient population that is expected to receive nivolumab in clinical practice.

A6. According to the CS, p. 30, the ratio of males to females affected by SCCHN is 2.4:1, which would, assuming an equal mortality rate, imply a prevalence of approximately 70% male. However, in the CheckMate 141 trial, 83.1% are male (Table 13 of the CS). In addition, the CheckMate 141 clinical study report (CSR) Figure 7.2.1-1 shows a large difference due to sex i.e., HR for overall survival (OS) of nivolumab versus individual investigator's choice therapies was 0.65 (95% (CI) 0.48, 0.88) for males and 0.93 (95% CI 0.47, 1.85) for female.

   a. Please explain how the CheckMate 141 trial is representative of the SCCHN population given this apparent discrepancy"

In other licensed indications for nivolumab, no concerns have been raised with regards to differing efficacy between males and females.[5-8] For example, in the European Public Assessment Report for locally-advanced squamous NSCLC after prior chemotherapy, it was noted that although "*most subjects were male… no difference in efficacy was observed based on gender*."[6] No difference in efficacy based on gender is expected in R/M SCCHN. The results of the subgroup analysis in CheckMate 141 should be interpreted with caution given the noted differences in the number of males and females. The subgroup analysis of OS for nivolumab versus IC in females was based on a small sample size (nivolumab, n=43 and IC, n=18), whereas, the subgroup analysis in males was based on a much larger sample size (nivolumab, n=197 and IC, n=103). As may be expected, the subgroup analysis in males produced a HR with much narrower CIs (0.65; 0.48, 0.88), compared to that conducted in females (0.93; 0.47, 1.85).[3] Additionally, the difference in the ratio of men/women in CheckMate-141 versus the ratio in the overall UK SCCHN patient population is assumed to be is due to random variation in a sample versus a population.

Correction: on inspecting the information presented in the CS, the ratio of males to females affected by SCCHN was found to be incorrect. Based on the Office for National Statistics Cancer Registration Statistics 2014[9] (ICD-10 codes C0–14 and C30–32), this ratio should be 2.24 rather than 2.4.

A7. According to Figure 7.2.1-1 in the CSR, there is a large difference in the OS HRs between North America and the European Union (EU), i.e. 0.55 (95% CI 0.36, 0.85) and 0.91 (95% CI 0.62, 1.33) respectively. explain this difference.

Given numerical differences in OS outcomes by region; baseline characteristics, demographics and investigator's choice of therapy have been explored by region. Patients randomised in North America, Europe, and Rest of World, had similar baseline characteristics and demographics, with few exceptions.

A lower percentage of patients randomised in Europe were human papilloma virus (HPV)-positive ([redacted]%) than in North America ([redacted]%). Furthermore, in Europe, an imbalance in HPV positivity was observed between the two arms; [redacted]% of patients in the nivolumab arm versus

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[redacted]% in the IC arm. This imbalance is important because, in the all-treated (ITT) population, HPV positive status was associated with greater magnitude of effect on OS and HPV is a known prognostic factor, regardless of treatment.[10, 11] To further explore the contribution of this imbalance to the findings in the European subgroup, a Cox model of survival on treatment and HPV status (positive, negative, not reported) was generated for European patients. The HR of nivolumab versus IC from this model, adjusted for HPV status, was [redacted]) compared to HR = [redacted] in the unadjusted analysis, suggesting that the imbalance in HPV status may have contributed to the outcome observed in European patients.

In Europe, the percentage of patients who never smoked was less than that in North America ([redacted]% versus [redacted]%). However, smoking status was balanced across both arms. In the ITT population, "never smoker" status was associated with numerically higher effect on OS than "current or former smoker" status (OS HR of 0.58 [95% CI: 0.32, 1.06] versus 0.71 [95% CI: 0.52, 0.99]).[10] Never smokers are expected to be more frequently HPV positive,[12] and the outcome by smoking status in CheckMate-141 may be driven by differences in HPV. 1 Of note, in NSCLC, smokers appear to have a greater magnitude of benefit from immunotherapy.[5]

The selection of IC also differed by region, probably reflecting clinical practice.[3] In North America, of the [redacted] patients randomised to the IC arm, [redacted]%) patients received methotrexate, while [redacted]%) patients received cetuximab and [redacted]%) patients were treated with docetaxel.[3] In contrast, of the [redacted] patients randomized to the control arm in Europe, the majority were treated with docetaxel ([redacted] patients, [redacted]%) and the remainder ([redacted] patients, [redacted]%) received methotrexate.[3]

In summary, several factors may have affected the European subgroup OS outcome, including the lower proportion of HPV-positive patients, an imbalance of HPV status across treatment arms within the European subgroup, the smaller never smoker population in Europe, and differences in choice of IC of therapy (i.e., a preference for docetaxel).

A8. The CheckMate 141 trial treated patients with docetaxel at a dose of 30 mg/m^2 every week, but, as stated in the CS, is prescribed every 3 weeks.[1] Indeed, the latest United Kingdom National Multidisciplinary Guidelines Head and Neck Cancer, p. S187, recommend a regimen of 75-100 mg/m^2 every 3 weeks.

a. Please explain why the weekly regimen was chosen for the CheckMate 141 trial.

As stated in the study protocol for CheckMate 141, weekly dosing of docetaxel was used in the CheckMate 141 trial based on previous evidence of clinical activity at this dose and schedule in SCCHN.[3]

Feedback from clinical experts was that neither dosing schedule is considered superior in terms of efficacy and both posologies are in fact used in clinical practice. The decision of which schedule to use would be based on the physician's choice and consultation with the patient. It would be influenced by the patient convenience and the risk of developing or exacerbating complications known to be associated with docetaxel use e.g., neutropenia. Fitter patients would

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typically be treated with 3-weekly docetaxel, and less fit, elderly patients would be treated with weekly dosing, which would be considered better tolerated in terms of toxicity.

There is no direct comparable evidence for weekly vs. 3-weekly dosing of docetaxel specifically in SCCHN. However, the two posologies have been compared in other indications, which found no difference in efficacy in terms of overall survival, but a significantly lower rate of toxicity with the weekly schedule (see answer b below for further details).

b. Please provide evidence as to the relative efficacy of weekly vs. 3 weekly administrations.

In a phase III trial, 259 patients with advanced NSCLC were randomised to receive either docetaxel 75mg/m2 every 3 weeks, or docetaxel 36 mg/m2 every week for 6 weeks followed by 2 weeks of rest.[13] One-year survival was 27% in the 3-weekly arm and 22% in the weekly arm, and median time to progression was also similar in the two arms. In terms of toxicity however, the rate of febrile neutropenia was significantly higher in the 3-weekly arm compared with the weekly arm (7.8% vs. 0.8%, $p<0.01$).[13]

In a phase II trial, 125 patients with locally-advanced or metastatic NSCLC were randomised to receive either docetaxel 75mg/m2 every 3 weeks, or docetaxel 40 mg/m2 every week for 6 weeks followed by 2 weeks of rest.[14] Median time to progression and survival were rather similar in both arms, respectively: 2.1 months and 5.8 months for patients in the 3-weekly arm, and 1.8 months and 5.5 months for patients in the weekly dosing arm. Similarly, a significantly lower rate of severe neutropenia was observed in the weekly arm.[14]

As such, the use of weekly docetaxel dosing in CheckMate 141 can be considered a conservative approach within this economic evaluation for nivolumab, since it utilised a dosing regimen for docetaxel that can be considered to be of equivalent efficacy and likely to be less toxic than that used in clinical practice.

A9. Section 4.11 of the CS contains no evidence.[1] However, four non-controlled studies of paclitaxel were reported in Table 17 of the CS. Also, one randomised control trial (RCT) with paclitaxel as one of the arms was also reported in Table 17. Although, no indirect comparison is possible, it would be useful to see the results of these studies in order to help to validate the claim that there is no difference between paclitaxel and any of the therapies in the Investigator Choice arm of the CheckMate 141 trial. Please provide a review of these five studies, including any results for OS and PFS.

A summary of the methodology of the five studies is provided in Table 6. Table 7 presents the baseline characteristics across these studies, and Table 8 presents a summary of outcomes in terms of tumour response, PFS and OS.

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Table 6: Summary of methodology of five paclitaxel studies

Trial	Trial design	Population	Intervention	Comparator(s)	Primary study reference; *Secondary study reference(s)*
BERIL-1	Phase II, randomised study	Patients with platinum pre-treated R/M SCCHN	Paclitaxel (i.v. 80 mg/m^2 weekly) plus placebo; n=79	Paclitaxel (i.v. 80 mg/m^2 weekly) plus buparlisib (oral 100mg daily); n=79	Soulieres (2016),[15] *Licitra (2016)*[16]
Tahara (2011)	Phase II, single-arm study	Patients with R/M SCCHN and one or no prior chemotherapy regimens	Paclitaxel (i.v. 100 mg/m^2 once weekly for 6 weeks of a 7-week cycle); n=74	N/A	Tahara (2011)[17]
Caballero (2007)	Before-and-after study	Patients with R/M SCCHN refractory to platinum-based therapies	Paclitaxel (i.v. 80 mg/m^2 once weekly for 6 weeks); n=33	N/A	Caballero (2007)[18]
Grau (2009a)	Phase II, single-arm study	Patients with platinum-resistant R/M SCCHN	Paclitaxel (i.v. 80 mg/m^2 once weekly for 6 weeks); n=60	N/A	Grau (2009a)[19]
Grau (2009b)	Single-arm study	Patients with SCCHN and progression following platinum-based chemotherapy	Paclitaxel (i.v. 80 mg/m^2 once weekly for 6 weeks); n=47	N/A	Grau (2009b)[20]

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Table 7: Summary of baseline characteristics across the five paclitaxel studies

	Tahara 2011	BERIL-1 (BUP + PAC)	BERIL-1 (PAC + PBO)	Caballero 2007	Grau 2009a	Grau 2009b
Gender (n [%])						
Male	56 (77.8)	NR	NR	30 (91)	55 (91.7)	4 (8.5)
Female	16 (22.2)	NR	NR	3 (9)	5 (8.3)	43 (92.5)
Age (median ([range])	61 (41–74)	59 (NR)	58 (NR)	58 (46–80)	59.5 (45–79)	57 (46–80)
ECOG PS (n [%])						
0	48 (66.7)	NR	NR	0 (0)	1 (1.7)	1 (2.1)
1	22 (30.6)	NR	NR	29 (88)	50 (83.3)	37 (78.7)
2	2 (2.8)	NR	NR	4 (12)	9 (15.0)	9 (19.1)
Disease status (n [%])						
Advanced (metastatic)	25 (34.7)	NR	NR	12 (36)	13 (21.7)	16 (34.0)
Recurrent	47 (65.3)	NR	NR	14 (43)	31 (51.7)	27 (57.4)
Both	NR	NR	NR	7 (21)	16 (26.4)	4 (8.5)
Primary location (n [%])						
Oral cavity	8 (11.1)	NR	NR	10 (30)	NR	12 (25.5)
Paranasal cavity	8 (11.1)	NR	NR	NR	NR	NR
Nasopharynx	8 (11.1)	NR	NR	NR	NR	NR
Oropharynx	12 (16.7)	NR	NR	12 (37)	30 (50)	12 (25.5)
Hypopharynx	18 (25.0)	NR (29)	NR (39)	NR	10 (16.7)	7 (14.9)
Larynx	6 (8.3)			NR	20 (33.3)	NR
Salivary gland	7 (9.7)	NR	NR	NR	NR	NR
Supraglottis	NR	NR	NR	6 (18)	NR	10 (21.3)
Glottis	NR	NR	NR	5 (15)	NR	6 (12.8)
Prior treatment						
Chemotherapy[a]	62 (86.1)	NR	NR	NR	32 (53.3)[b]	47 (100)

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Platinum-based chemotherapy	55 (76.4)	NR	NR	NR		
Surgery	36 (50.0)	NR	NR	NR	38 (62.3)	
Radiotherapy	60 (83.3)	NR	NR	NR	15 (24.6)	
Chemotherapy plus radiotherapy	NR	NR	NR	NR	7 (11.5)	
Other	7 (9.7)	NR	NR	NR	NR	

[a] Including adjuvant chemotherapy, neoadjuvant chemotherapy, and chemoradiotherapy
[b] Previous palliative chemotherapy

Table 8: Summary of outcomes across the five paclitaxel studies

	Tahara 2011	BERIL-1 (BUP + PAC)	BERIL-1 (PAC + PBO)	Cabellero 2007	Grau 2009a	Grau 2009b
Objective response rate (Complete response + partial response + stable disease)	30.4%	39%	14%	61%	58.3%	NR
Median PFS (95% CI)	3.2 months (2.5–6.7)	4.6 months (NR)	3.5 months (NR)	NR	6.2 months (3.7 – 8.6) (responding patients)	5.1 months (NR) (responding patients)
Median OS (95% CI)	11.4 months (7.4–19.4)	10.0 months (NR)	6.5 months (NR)	NR	8.5 months (5.7–11.2) (responding patients) 3.4 months (2.0–4.9) (non-responding patients)	5.6 months (NR)

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A10. The CS states on p. 89 that *'The next database lock of the CheckMate 141 trial is expected in* [redacted] *from which updated efficacy analyses will be conducted.'*[1] Please confirm whether the results of these analyses are available now and if so consider updating the current analyses to include all available data. If data is not available at present, please provide a date when this is expected.

Data from the next database lock of the CheckMate 141 trial is expected to be available on [redacted].

CiC highlighting: the database lock date included in the question should be marked as commercial in confidence. This marking has been added to the question in this response document.

A11. In Section 5.2.4 on p.98 the CS states: 'The treatment of patients beyond disease progression is consistent with the trial protocol for CheckMate 141 (see Section 4.3), and the licensed posology for nivolumab which states that "treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient."'

a. Please provide the definition of 'clinical benefit' used in the trial.

As detailed in Section 4.5.9 of the study protocol, patients in the nivolumab arm were permitted to continue treatment with nivolumab beyond initial RECIST-defined progression, as long as the following criteria were met:

- Investigator-assessed clinical benefit, and do not have rapid disease progression
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
- Patient provides written informed consent prior to receiving any additional nivolumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.[3]

A single definition of 'clinical benefit' is not provided in the protocol. However, it is noted that the assessment of clinical benefit should have taken into account whether the patient was clinically deteriorating and unlikely to receive further benefit from continued treatment.[3]

Generally, clinical benefit in this context is based on both objective and subjective information. The decision to discontinue therapy requires considerable clinical competence, judgment and clear discussions and involvement of the patient. Beyond frank, objective progression, if the patient is considered (in their own judgement and that of the treating physician) to have an improved quality of life, or at the very least to have maintained their quality of life, then they are allowed to continue treatment, as long as their disease is relatively stable and they are not experiencing any worsening of side effects (i.e., type, frequency or severity).

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b. Please verify whether this definition is in line with current UK clinical practice.

The approach described in response to Question A11a to assess whether a patient is experiencing clinical benefit is believed to closely resemble day-to-day clinical practice and is an important factor in deciding whether to stop and/or change therapy.

Section B: Clarification on cost-effectiveness data

Treatment effectiveness

B1. **Priority:** the coefficients and parameterisations of the time-to-event models were not provided either in the CS or in the economic model.[1] Moreover, these parameters were not incorporated in the probabilistic sensitivity analysis (PSA).

a. Please provide the coefficients used to estimate OS, PFS and TTD in the model (for all different distributions), as well as the covariance matrix.

b. Please provide the formulas used to estimate OS, PFS and TTD in the model (for all different distributions).

c. Please incorporate the time-to-event models used to estimate OS, PFS and TTD in the model as probabilistic parameters in the probabilistic sensitivity analyses of the CS base-case and all requested analyses in this clarification letter.

d. Please provide an updated model including these amendments.

A revised copy of the originally submitted model has been provided along with this response. In this revised version of the model, the following changes relating to Question B1 and some later questions have been made:

- Co-efficients used to estimate OS, PFS and TTD have been incorporated
- Covariance matrices have been supplied for information
- Parameterised curves for OS, PFS and TTD have been derived directly from formulae as equations within the model for all non-spline curves
- The probabilistic sensitivity analysis has been updated to incorporate standard deviations for survival model parameters (Question B10)
- The deterministic sensitivity analysis has been updated to include survival model parameters
- The probabilistic sensitivity analysis has been updated to incorporate measures of variance based on empirical data (e.g., based on quartiles provided for some NHS reference costs) where available (Question B10)
- Disaggregated life years by health states for nivolumab and all comparators programmed as model outputs (Question B11)
- The cost-effectiveness acceptability curve has been updated to include multiple comparators (Question B13)

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This model is described as the “revised base case model”. Based on these model adjustments, there are no changes to the deterministic results presented for our original model and this revised base case. However, results of deterministic and probabilistic sensitivity analyses have changed and are reported in response to Question B10. Furthermore, disaggregated life years are now available and these are reported in response to Question B13.

B2. **Priority:** In the CS, equivalent effectiveness of docetaxel and methotrexate is assumed.[1] However, the references provided by the company to justify this assumption indicated that methotrexate is marginally less effective than docetaxel (clinical expert opinion) and that methotrexate has a statistically significant lower response than docetaxel (randomised phase II trial in patients with recurrent head and neck cancer).

a. Please provide a revised version of section 5.3 of the CS (including OS, PFS, TTD and AEs) relaxing the assumption of equivalent effectiveness of docetaxel and methotrexate. More specifically use treatment specific effectiveness estimates for docetaxel and methotrexate, while using the matched ‘intended investigator’s choice’ as a covariate for the nivolumab comparator. Please also provide the rationale as to why this analysis has not been done.

In considering the reference (Guardiola 2004) noted in this question, our opinion is that the support of this reference for equivalent effectiveness of docetaxel and methotrexate in terms of PFS and OS is valid. Although response rates were noted as significantly different between the two therapies, the authors of this paper use the term “super-imposable” to describe a comparison of both overall survival and time to progression on docetaxel and methotrexate.[21] This is a strong word to have been used in a scientific paper and indicates a clear conclusion from the authors that no differences existed in time to progression and overall survival between the two therapies based on the results of this study.

An analysis using treatment specific effectiveness estimates for methotrexate and docetaxel was not performed originally because it results in reduced sample sizes and also breaks the randomisation of the CheckMate-141 trial, meaning that both observable and unobservable patient baseline characteristics may no longer be balanced across comparison groups. Given that the Guardiola 2004 paper supports an assumption of equivalent effectiveness of docetaxel and methotrexate with regards to overall survival and time to progression, and UK clinical feedback confirmed the appropriateness of this assumption, the maintenance of statistical power and randomisation by using the IC arm of the whole was considered the most appropriate approach.

Nevertheless, in response to this request, a scenario analysis has been conducted to explore treatment specific effectiveness estimates for docetaxel and methotrexate. In this scenario analysis, survival curves have been parameterised for the subgroups of the CheckMate-141 trial as follows:

- Patients who received docetaxel (to model docetaxel efficacy and paclitaxel efficacy)

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- Patients who received methotrexate (to model methotrexate efficacy)
- Nivolumab patients who would otherwise have received docetaxel (i.e. the nivolumab-matched population for docetaxel)
- Nivolumab patients who would otherwise have received methotrexate (i.e. the nivolumab-matched population for methotrexate)

Discussion of the parameterisation of these curves in line with Section 5.3 of our original submission is provided below.

Matched nivolumab versus docetaxel

Details are provided below for the survival analysis informing the two scenario analyses in which treatment-specific effectiveness estimates were used for docetaxel and methotrexate, respectively, versus matched nivolumab. These treatment-specific estimates were derived from the relevant subgroups of the CheckMate-141 study. The same approach to choosing the most appropriate parametric survival distribution for each of the clinical parameters (OS, PFS, TTD) as described in the original CS, was used for these scenario analyses. Consideration was given to the statistical fit and the clinical plausibility associated with each distribution, in addition to the relationships between the OS, PFS and TTD curves, and the long-term mortality rate associated with the chosen OS distribution versus general population mortality.

The full range of parametric survival distributions specified in the DSU were explored as independent models for OS of nivolumab and comparator efficacy. As per the original submission, spline-based models were explored but were not favoured where non-spline-based models demonstrated sufficient fit and clinically plausible results. Although spline-based models can demonstrate strong statistical fit, they can potentially over fit the trial data and have the potential to introduce increased complexity where it is not warranted.

Overall survival: matched nivolumab versus docetaxel

A summary of the AIC and BIC values for each of the independent parametric distributions explored for OS for matched nivolumab and docetaxel is provided in Table 9 and Table 10 below.

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Table 9: Summary of goodness-of-fit data for matched nivolumab OS models

Distribution	AIC	BIC
Exponential	326.6913	329.1686
Weibull	328.0338	332.9885
Gamma	328.5221	333.4768
Gompertz	323.5480	328.5027
Lognormal	320.0350	324.9896
Loglogistic	322.9240	327.8786
Generalised-gamma	318.7812	326.2133
Spline models:		
1-spline hazard	317.9774	325.4094
1-spline odds	318.1475	325.5795
1-spline normal	318.5011	325.9331
2-spline hazard	320.0077	329.9170
2-spline odds	320.0283	329.9377
2-spline normal	319.6877	329.5970

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

Table 10: Summary of goodness-of-fit data for docetaxel OS models

Distribution	AIC	BIC
Exponential	225.4484	227.4374
Weibull	221.9076	225.8856
Gamma	220.9674	224.9454
Gompertz	225.0448	229.0228
Lognormal	220.2978	224.2758
Loglogistic	220.4043	224.3822
Generalised-gamma	222.1110	228.0780
Spline models:		
1-spline hazard	222.1448	228.1117
1-spline odds	222.3695	228.3364
1-spline normal	222.0759	228.0429
2-spline hazard	224.0272	231.9831
2-spline odds	224.3573	232.3133
2-spline normal	223.9361	231.8921

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

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The chosen parametric distribution for nivolumab and docetaxel OS was the lognormal distribution based on the following:

- Although the best-fitting for nivolumab, the spline models were not considered further for the base case because the non-spline models such as the generalised-gamma and the lognormal had similar AIC/BIC values to them, and, for docetaxel, these non-spline models were the best-fitting. The added complexity of these models was therefore considered unnecessary given the AIC/BIC values across both arms
- Lognormal was the best fitting distribution overall for docetaxel, and the second-best fitting non-spline distribution for nivolumab
- The best-fitting non-spline model for nivolumab was the generalised-gamma, which was associated with a mean OS for nivolumab of 39.29 months, which was considered clinically implausible.
- The lognormal distribution was associated with a mean OS of 20.1 months for nivolumab, and 9.7 months for docetaxel.
- The lognormal distribution was also used in the original base case of the CS, which was associated with a mean OS of 17.7 months for nivolumab, and 8.4 months for the IC arm.

The long-term extrapolation of the non-spline models for OS with nivolumab and docetaxel are presented in Figure 9 and Figure 10 below.

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Figure 9: Long-term extrapolation of non-spline models for OS - nivolumab

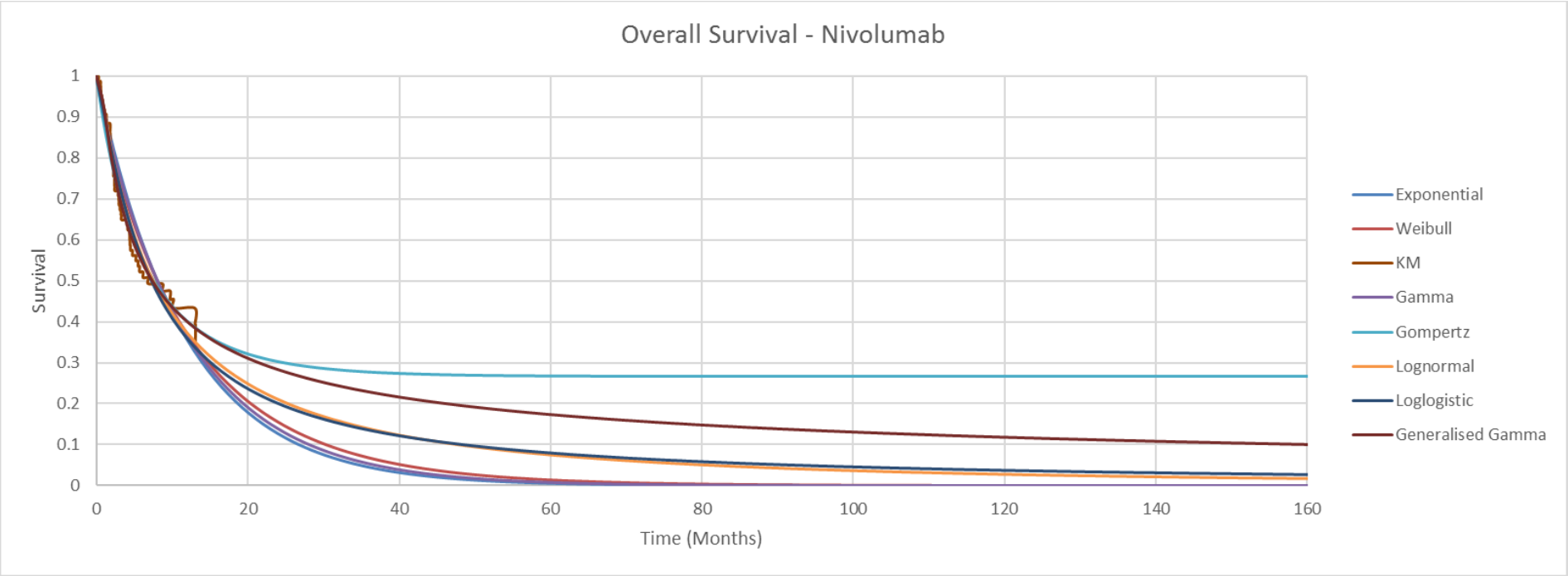

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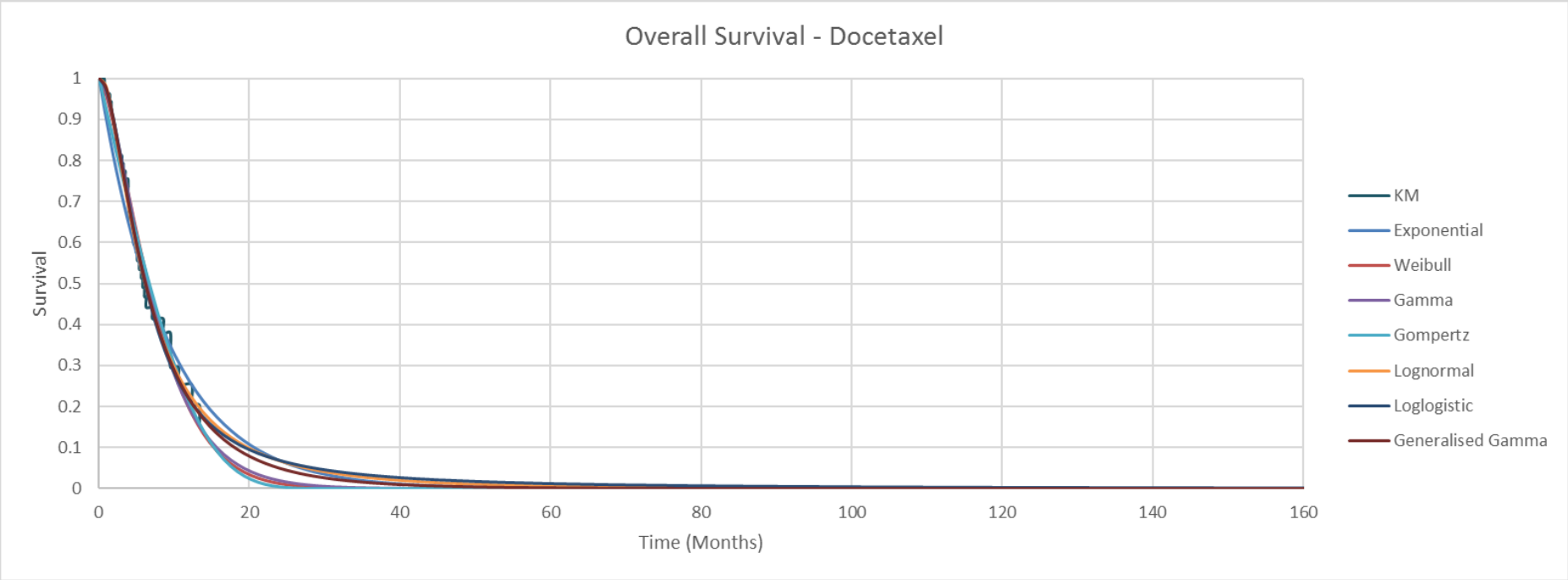
Figure 10: Long-term extrapolation of non-spline models for OS - docetaxel



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Progression-free survival: matched nivolumab versus docetaxel

A summary of the AIC and BIC values for each of the independent parametric distributions explored for PFS for matched nivolumab and docetaxel is provided in Table 11 and Table 12 below.

Table 11: Summary of goodness-of-fit data for matched nivolumab PFS models

Distribution	AIC	BIC
Exponential	326.2593	328.7367
Weibull	327.5106	332.4652
Gamma	325.0869	330.0415
Gompertz	326.2528	331.2075
Lognormal	307.8877	312.8424
Loglogistic	307.9043	312.8589
Generalised-gamma	303.9404	311.3724
Spline models:		
1-spline hazard	298.9035	306.3355
1-spline odds	298.0419	305.4739
1-spline normal	301.1759	308.6079
2-spline hazard	NE	NE
2-spline odds	297.7370	307.6464
2-spline normal	297.1566	307.0660

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

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Table 12: Summary of goodness-of-fit data for docetaxel PFS models

Distribution	AIC	BIC
Exponential	206.4163	208.4053
Weibull	197.9248	201.9027
Gamma	195.9251	199.9031
Gompertz	204.3923	208.3703
Lognormal	196.6256	200.6036
Loglogistic	194.6100	198.5880
Generalised-gamma	197.2944	203.2614
Spline models:		
1-spline hazard	197.1195	203.0864
1-spline odds	196.3129	202.2799
1-spline normal	196.9633	202.9303
2-spline hazard	198.4940	206.4500
2-spline odds	198.2790	206.2349
2-spline normal	198.2504	206.2063

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

The chosen parametric distribution for nivolumab and docetaxel PFS was the loglogistic distribution based on the following:

- The generalised gamma distribution was the best-fitting non-spline model for nivolumab and amongst the best-fitting for docetaxel. However, this curve was associated with a mean PFS of 6.45 months, which was considered much higher than the PFS from the original base case in the CS (4.7 months). As this estimate of PFS with nivolumab had been validated with clinical experts it was considered inappropriate to choose a distribution providing such a differing PFS when other distributions with only marginally worse fit were available.
- As such, the second-best fitting non-spline model was chosen, which was the loglogistic. The loglogistic distribution was associated with a mean PFS of 4.8 months for nivolumab and 4.4 months for docetaxel, which were considered close to those from the original base case used in the CS, which was associated with a mean PFS of 4.6 months for nivolumab and 3.6 months for the IC arm.

The long-term extrapolation of the non-spline models for PFS with nivolumab and docetaxel are presented in Figure 11 and Figure 12 below.

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Figure 11: Long-term extrapolation of non-spline models for PFS - nivolumab

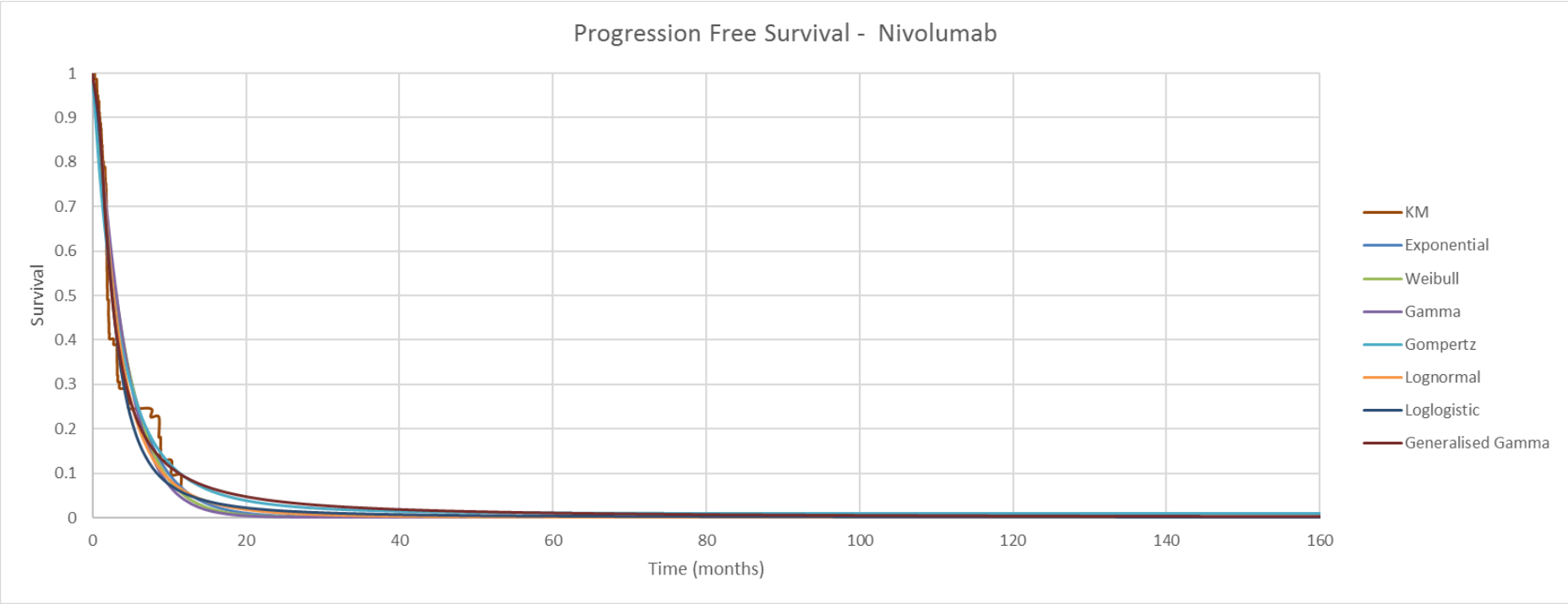

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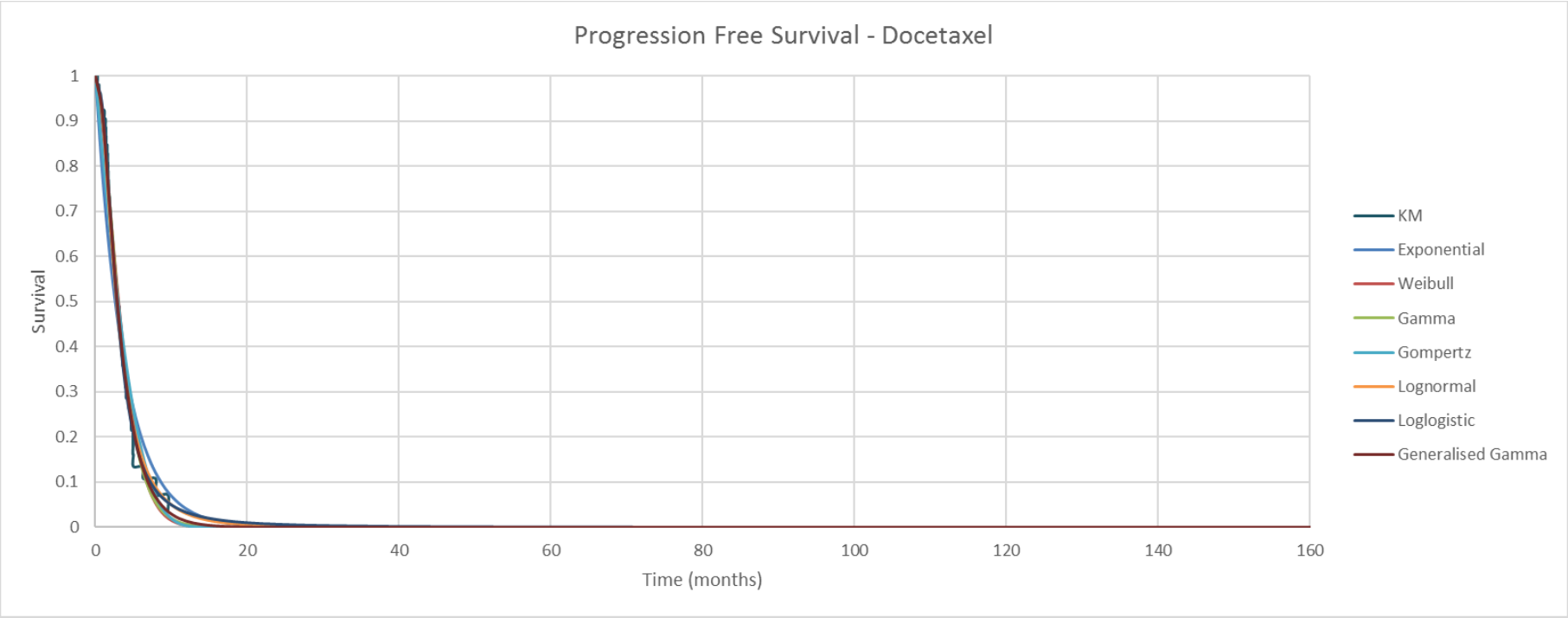
Figure 12: Long-term extrapolation of non-spline models for PFS - docetaxel



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Time to treatment discontinuation: matched nivolumab versus docetaxel

A summary of the AIC and BIC values for each of the independent parametric distributions explored for TTD for matched nivolumab and docetaxel is provided in Table 13 and Table 14 below.

Table 13: Summary of goodness-of-fit data for matched nivolumab TTD models

Distribution	AIC	BIC
Exponential	373.6459	376.1233
Weibull	375.3007	380.2554
Gamma	373.4198	378.3745
Gompertz	372.1989	377.1535
Lognormal	355.4967	360.4513
Loglogistic	355.7339	360.6885
Generalised-gamma	351.5016	358.9336
Spline models:		
1-spline hazard	346.8247	354.2567
1-spline odds	346.6679	354.0999
1-spline normal	349.4895	356.9215
2-spline hazard	348.9722	358.8815
2-spline odds	347.8457	357.7551
2-spline normal	347.6678	357.5771

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

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Table 14: Summary of goodness-of-fit data for docetaxel TTD models

Distribution	AIC	BIC
Exponential	219.6807	221.6320
Weibull	203.2644	207.1669
Gamma	199.1141	203.0166
Gompertz	213.3939	217.2964
Lognormal	197.4977	201.4002
Loglogistic	196.4116	200.3141
Generalised-gamma	199.2830	205.1368
Spline models:		
1-spline hazard	198.4105	204.2642
1-spline odds	198.4046	204.2583
1-spline normal	199.2840	205.1377
2-spline hazard	200.1748	207.9798
2-spline odds	200.3986	208.2036
2-spline normal	200.2195	208.0244

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

The chosen parametric distribution for nivolumab and docetaxel TTD was the lognormal distribution based on the following:

- Whilst spline-based models did offer better statistical fit than non-spline models for the nivolumab TTD curve, they did not necessarily offer better statistical fit for the docetaxel comparator. For the reasons outlined in the CS Section 5.3, spline models were excluded from consideration where a simpler model provided a sufficient fit to the data.
- Considering the non-spline models only, the lognormal, loglogistic and generalised gamma were the next best fitting across both model arms and were of similar fit to each other.
- The best-fitting non-spline model for nivolumab was the generalised gamma but this was associated with a mean TTD of [redacted], which was [redacted] than the mean TTD for nivolumab from the base case. As mean TTD with nivolumab in the original base case had been validated with clinical opinion, such a rise in anticipated mean TTD with nivolumab was considered implausible.
- Of the lognormal and loglogistic distributions, the former was a slightly better fit for nivolumab and the latter a slightly better fit for docetaxel, though in both cases the differences in AIC values were negligible.
- Since the TTD curve for nivolumab was likely to have a greater impact on the ICER than that for docetaxel, the lognormal distribution was chosen, since this had the slightly better fit for nivolumab.
- The lognormal distribution was associated with a mean TTD of [redacted] for nivolumab and 3.6 months for docetaxel, which were considered close to those from the original base case

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used in the CS, which was associated with a mean TTD of [redacted] for nivolumab and 3.6 months for the IC arm, and therefore still suitably aligned with clinical opinion.

The long-term extrapolation of the non-spline models for TTD with nivolumab and docetaxel are presented in Figure 13 and Figure 14 below.

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Figure 13: Long-term extrapolation of non-spline models for TTD - nivolumab

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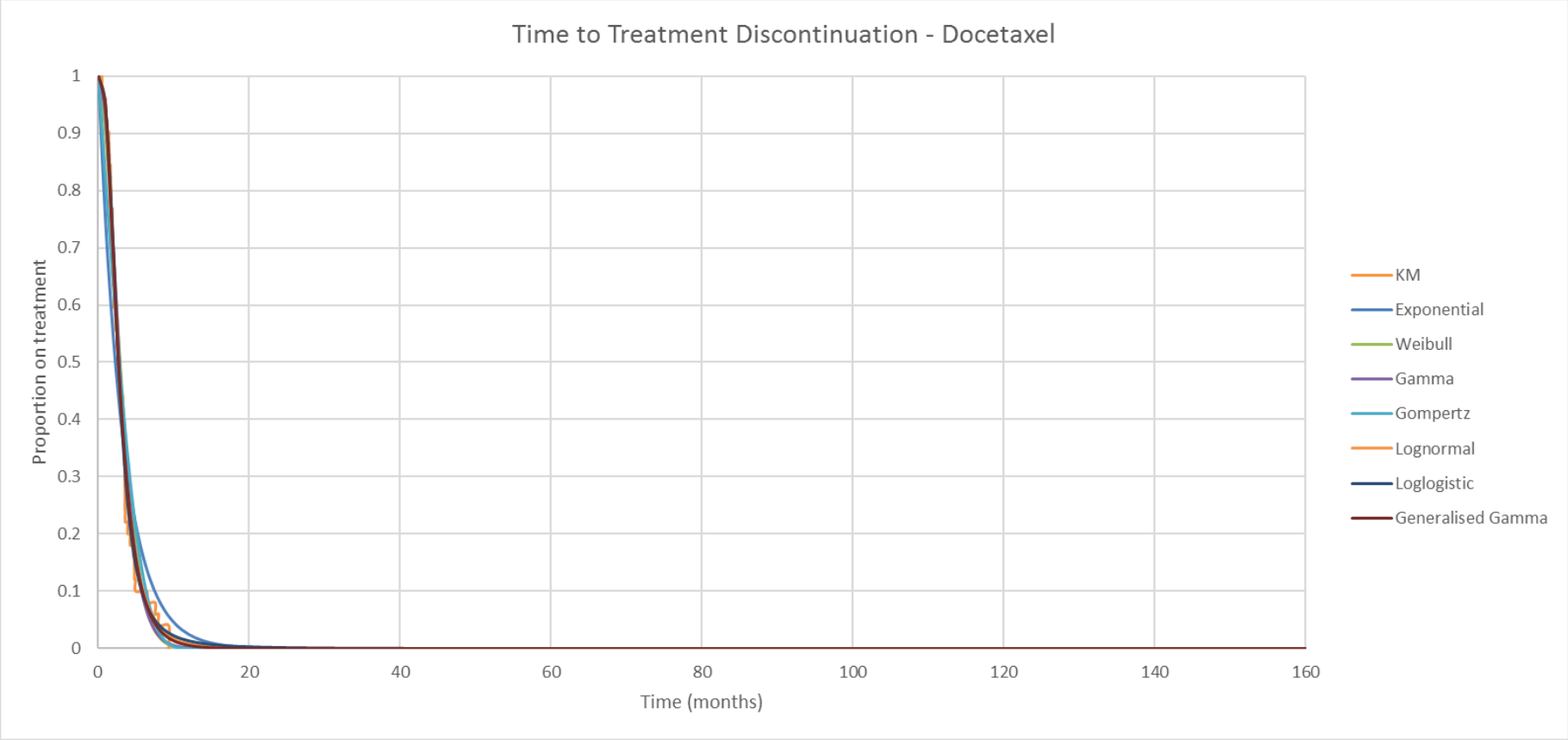
Figure 14: Long-term extrapolation of non-spline models for TTD – docetaxel



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Matched nivolumab versus methotrexate

Overall survival: matched nivolumab versus methotrexate

A summary of the AIC and BIC values for each of the independent parametric distributions explored for OS for matched nivolumab and methotrexate is provided in Table 15 and Table 16 below.

Table 15: Summary of goodness-of-fit data for matched nivolumab OS models

Distribution	AIC	BIC
Exponential	455.4451	458.2242
Weibull	457.3508	462.909
Gamma	457.1934	462.7517
Gompertz	457.3529	462.9112
Lognormal	455.4053	460.9636
Loglogistic	455.8278	461.386
Generalised-gamma	457.0187	465.356
Spline models:		
1-spline hazard	456.6936	465.031
1-spline odds	457.4523	465.7896
1-spline normal	457.1570	465.4943
2-spline hazard	458.2453	469.3618
2-spline odds	458.782	469.8985
2-spline normal	459.059	470.1755

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

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Table 16: Summary of goodness-of-fit data for methotrexate OS models

Distribution	AIC	BIC
Exponential	218.3006	220.2518
Weibull	216.0011	219.9036
Gamma	215.4967	219.3991
Gompertz	218.1666	222.0691
Lognormal	215.9734	219.8759
Loglogistic	215.8994	219.8019
Generalised-gamma	217.2154	223.0691
Spline models:		
1-spline hazard	217.4247	223.2785
1-spline odds	217.6615	223.5152
1-spline normal	216.9928	222.8466
2-spline hazard	219.3944	227.1993
2-spline odds	219.4795	227.2845
2-spline normal	218.9521	226.757

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

The chosen parametric distribution for nivolumab and methotrexate OS was the lognormal distribution based on the following:

- Lognormal was the best fitting distribution overall for nivolumab, and the third-best fitting distribution overall for methotrexate. The only other model that was similarly well-fitting across both treatment arms was the loglogistic, but since the lognormal provided the best fit for nivolumab and a clinical plausible length of OS, the lognormal distribution was chosen.
- The lognormal distribution was associated with a mean OS of 16.2 months for nivolumab, and 7.4 months for methotrexate, which was considered close to the original base case of the CS, which was associated with a mean OS of 17.7 months for nivolumab, and 8.4 months for the IC arm.

The long-term extrapolation of the non-spline models for OS with nivolumab and methotrexate are presented in Figure 15 and Figure 16 below.

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Figure 15: Long-term extrapolation of non-spline models for OS - nivolumab

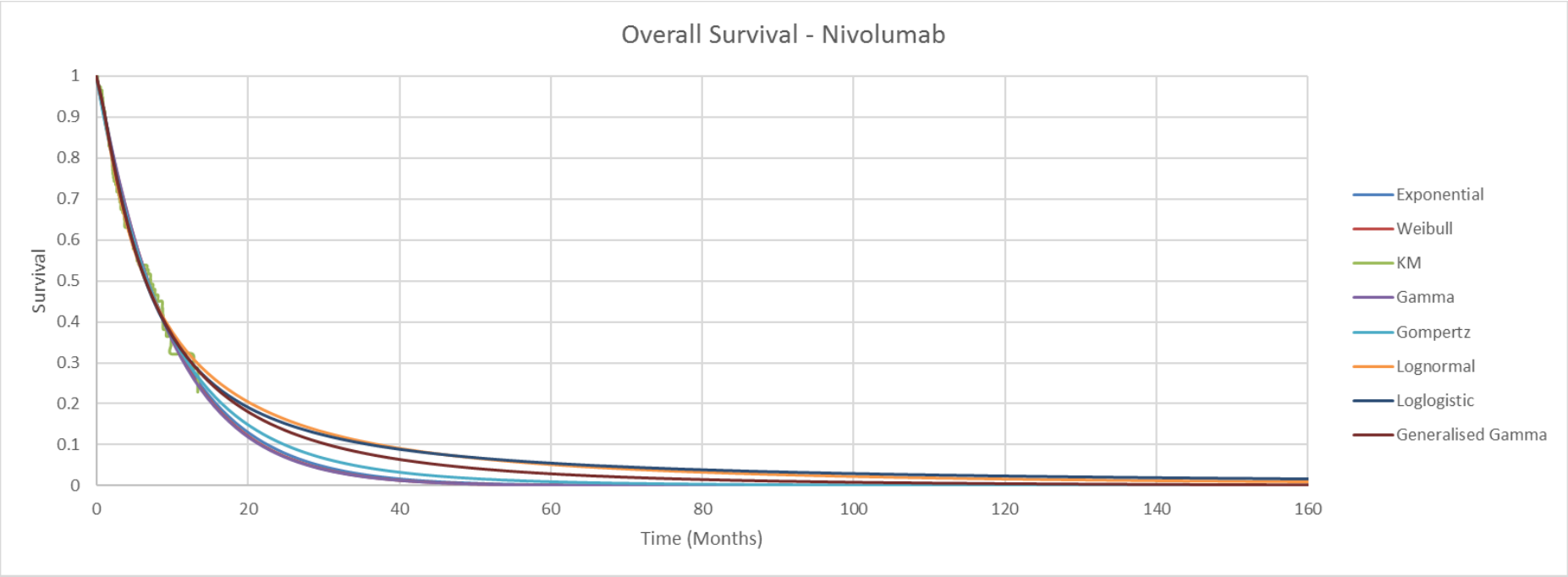

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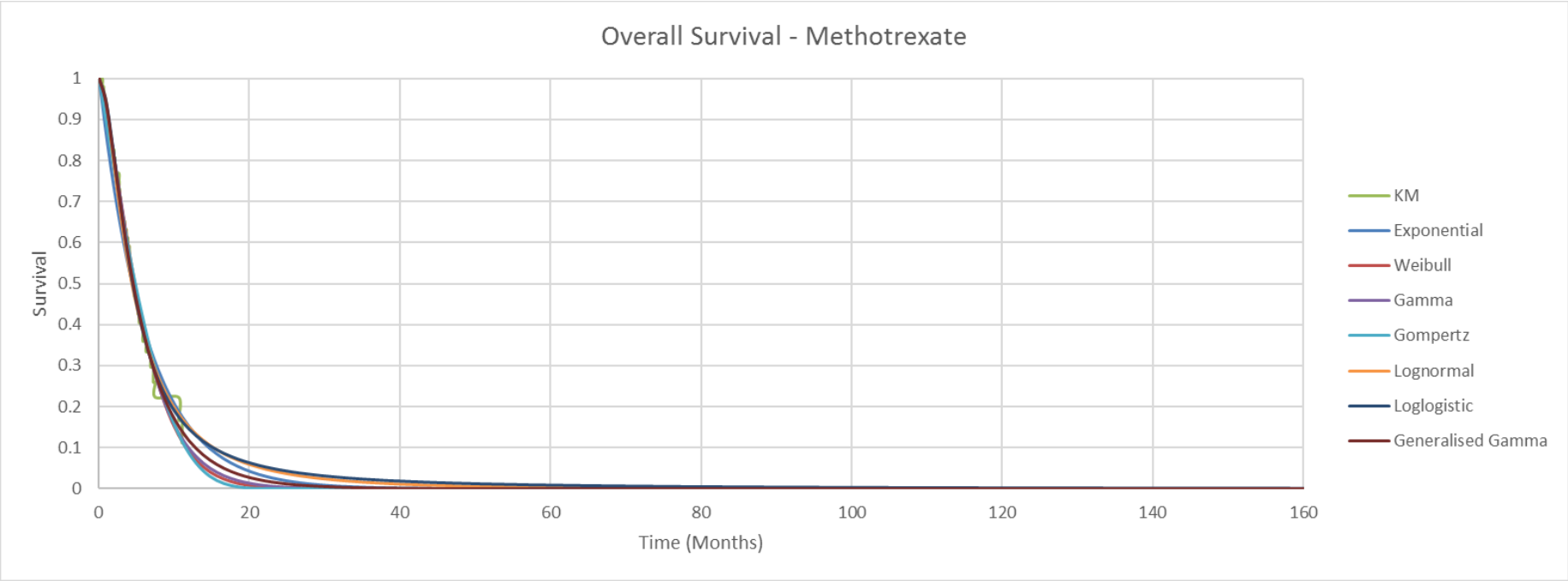
Figure 16: Long-term extrapolation of non-spline models for OS – methotrexate



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Progression-free survival: matched nivolumab versus methotrexate

A summary of the AIC and BIC values for each of the independent parametric distributions explored for PFS for matched nivolumab and methotrexate is provided in Table 17 and Table 18 below.

Table 17: Summary of goodness-of-fit data for matched nivolumab PFS models

Distribution	AIC	BIC
Exponential	437.051	439.8301
Weibull	433.1372	438.6954
Gamma	427.3656	432.9238
Gompertz	438.9712	444.5294
Lognormal	414.3628	419.9211
Loglogistic	406.5488	412.1071
Generalised-gamma	416.3604	424.6977
Spline models:		
1-spline hazard	405.6406	413.978
1-spline odds	405.9762	414.3136
1-spline normal	416.3476	424.6849
2-spline hazard	NE	NE
2-spline odds	387.2651	398.3816
2-spline normal	NE	NE

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

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Table 18: Summary of goodness-of-fit data for methotrexate PFS models

Distribution	AIC	BIC
Exponential	193.5188	195.4701
Weibull	182.6553	186.5578
Gamma	182.2931	186.1956
Gompertz	186.0509	189.9534
Lognormal	184.7341	188.6366
Loglogistic	185.9597	189.8622
Generalised-gamma	184.2892	190.1429
Spline models:		
1-spline hazard	184.2524	190.1061
1-spline odds	186.8479	192.7016
1-spline normal	184.6099	190.4637
2-spline hazard	185.7913	193.5963
2-spline odds	187.1345	194.9395
2-spline normal	185.7503	193.5553

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

The chosen parametric distribution for nivolumab and methotrexate PFS was the loglogistic distribution based on the following:

- The loglogistic distribution was the best-fitting of the non-spline models for the nivolumab arm and was also amongst the better fitting distributions for the methotrexate arm. Although some spline models were amongst the best fitting of the distributions for both arms, spline models were not considered based on the reasons mentioned previously, and those detailed in Section 5.3 of the CS.
- The loglogistic distribution was associated with a mean PFS of 3.8 months for nivolumab and 3.6 months for methotrexate which were considered close to those from the original base case used in the CS, which was associated with a mean PFS of 4.6 months for nivolumab and 3.6 months for the IC arm. As these estimates of PFS had been validated with clinical experts this consistency was considered to reinforce he choice of the loglogistic distribution for modelling PFS.
- As with the original base case, the choice of parametric distribution for PFS had very little, if any, impact on the overall ICER.

The long-term extrapolation of the non-spline models for PFS with nivolumab and methotrexate are presented in Figure 17 and Figure 18 below.

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Figure 17: Long-term extrapolation of non-spline models for PFS - nivolumab

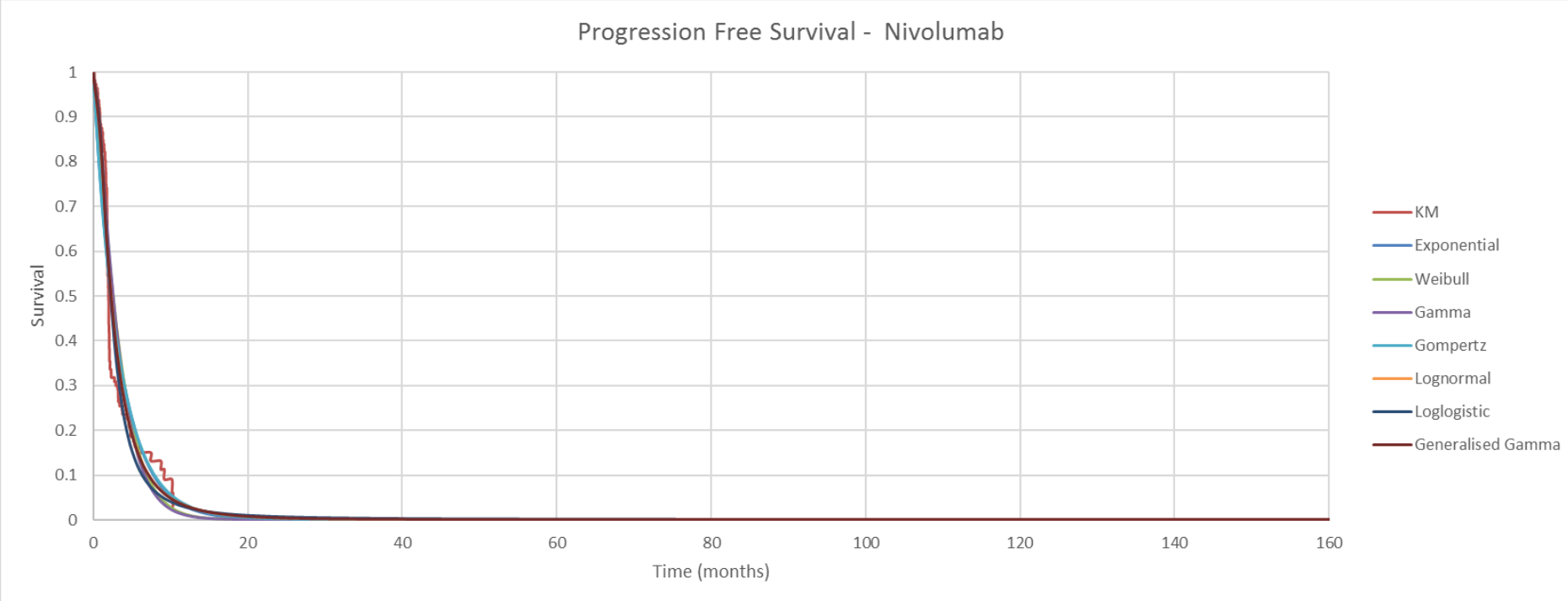

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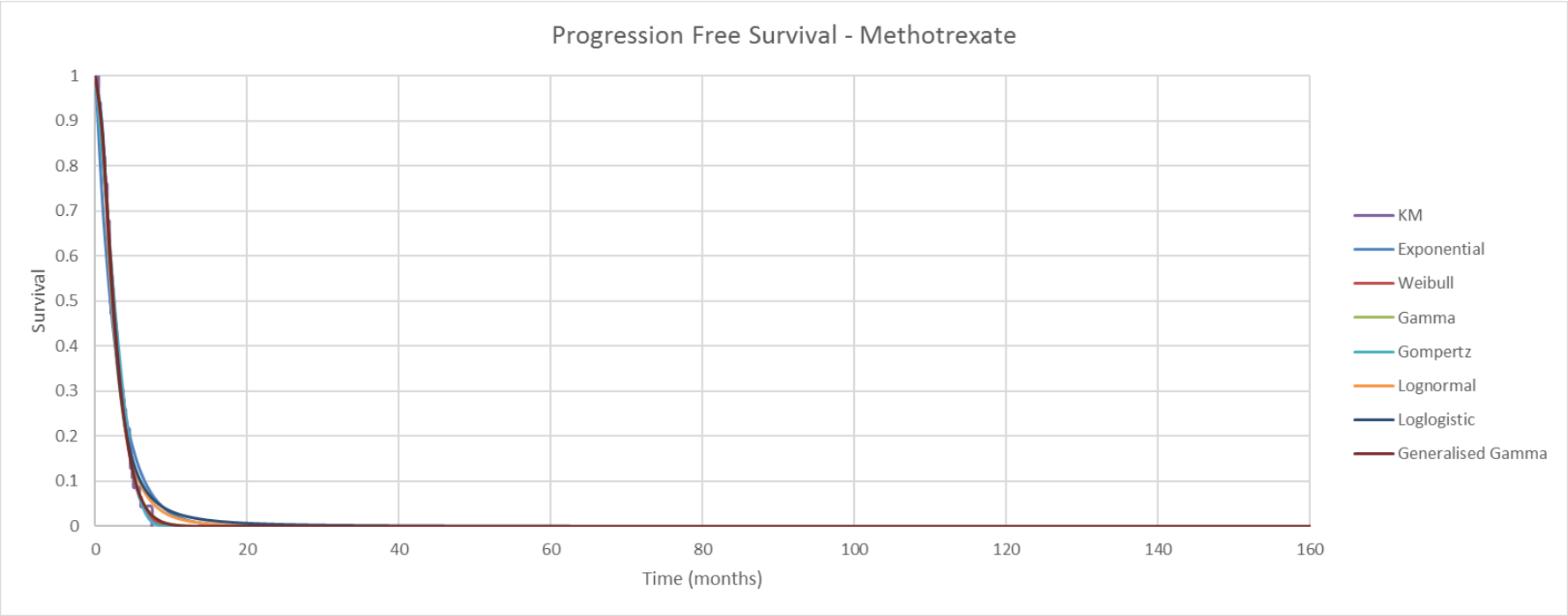
Figure 18: Long-term extrapolation of non-spline models for PFS – methotrexate



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Time to treatment discontinuation: matched nivolumab versus methotrexate

A summary of the AIC and BIC values for each of the independent parametric distributions explored for TTD for matched nivolumab and methotrexate is provided in Table 19 and Table 20 below.

Table 19: Summary of goodness-of-fit data for matched nivolumab TTD models

Distribution	AIC	BIC
Exponential	476.3381	479.0917
Weibull	475.5882	481.0953
Gamma	472.1824	477.6895
Gompertz	477.7901	483.2973
Lognormal	458.9512	464.4584
Loglogistic	456.4303	461.9374
Generalised-gamma	460.7018	468.9625
Spline models:		
1-spline hazard	453.5553	461.816
1-spline odds	453.8297	462.0905
1-spline normal	460.3641	468.6249
2-spline hazard	452.7732	463.7876
2-spline odds	450.8781	461.8925
2-spline normal	450.424	461.4384

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

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Table 20: Summary of goodness-of-fit data for methotrexate TTD models

Distribution	AIC	BIC
Exponential	173.6626	175.4912
Weibull	167.7390	171.3963
Gamma	168.2882	171.9455
Gompertz	168.6947	172.3520
Lognormal	175.5538	179.2111
Loglogistic	173.0961	176.7534
Generalised-gamma	169.7139	175.1998
Spline models:		
1-spline hazard	169.7390	175.2249
1-spline odds	172.3238	177.8097
1-spline normal	170.6795	176.1654
2-spline hazard	171.7360	179.0506
2-spline odds	173.7642	181.0788
2-spline normal	172.5513	179.8659

The distribution selected for the base is shaded grey
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

The chosen parametric distribution for nivolumab and methotrexate TTD was the loglogistic distribution based on the following:

- Spline-based models did not present markedly better fits for the IC arm and although they did provide the best fits for the nivolumab arm they were discounted based on reasons mentioned previously.
- Considering the non-spline models only, loglogistic, lognormal and generalised gamma were clearly the best fitting models for the nivolumab arm based on AIC values. There was little to choose between these, though the loglogistic model presented the best fit to the nivolumab data of the non-spline models
- In the IC arm, these three models were associated with similar fits to one another. They were not amongst the best fitting for the IC arm. However, the difference in AIC between these distributions and the best fitting non-spline models in the IC arm ranged from ~+2 to ~+8, whereas in the nivolumab arm these distributions were associated with a minimum of a ~12 point lower AIC than other non-spline options. Therefore, on balance, these three distributions were considered to have the best fit of the non-spline models across the two model arms.
- Given that TTD for nivolumab is a far greater driver of cost-effectiveness results than TTD of IC, fit to the nivolumab arm was prioritised over fit to the IC arm in deciding between these three distributions. As such, the loglogistic distribution was chosen.
- The loglogistic distribution was associated with a mean TTD of [redacted] for nivolumab and 3.5 months for methotrexate which were considered close to the those from the original base case used in the CS, which was associated with a mean TTD of [redacted] for nivolumab and 3.6 months for the IC arm. Furthermore, the mean TTD resulting from this choice of

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distribution seemed plausible versus the mean predicted PFS for nivolumab from the choice of base case PFS curve.

The long-term extrapolation of the non-spline models for PFS with nivolumab and methotrexate are presented in Figure 19 and Figure 20 below.

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Figure 19: Long-term extrapolation of non-spline models for TTD - nivolumab

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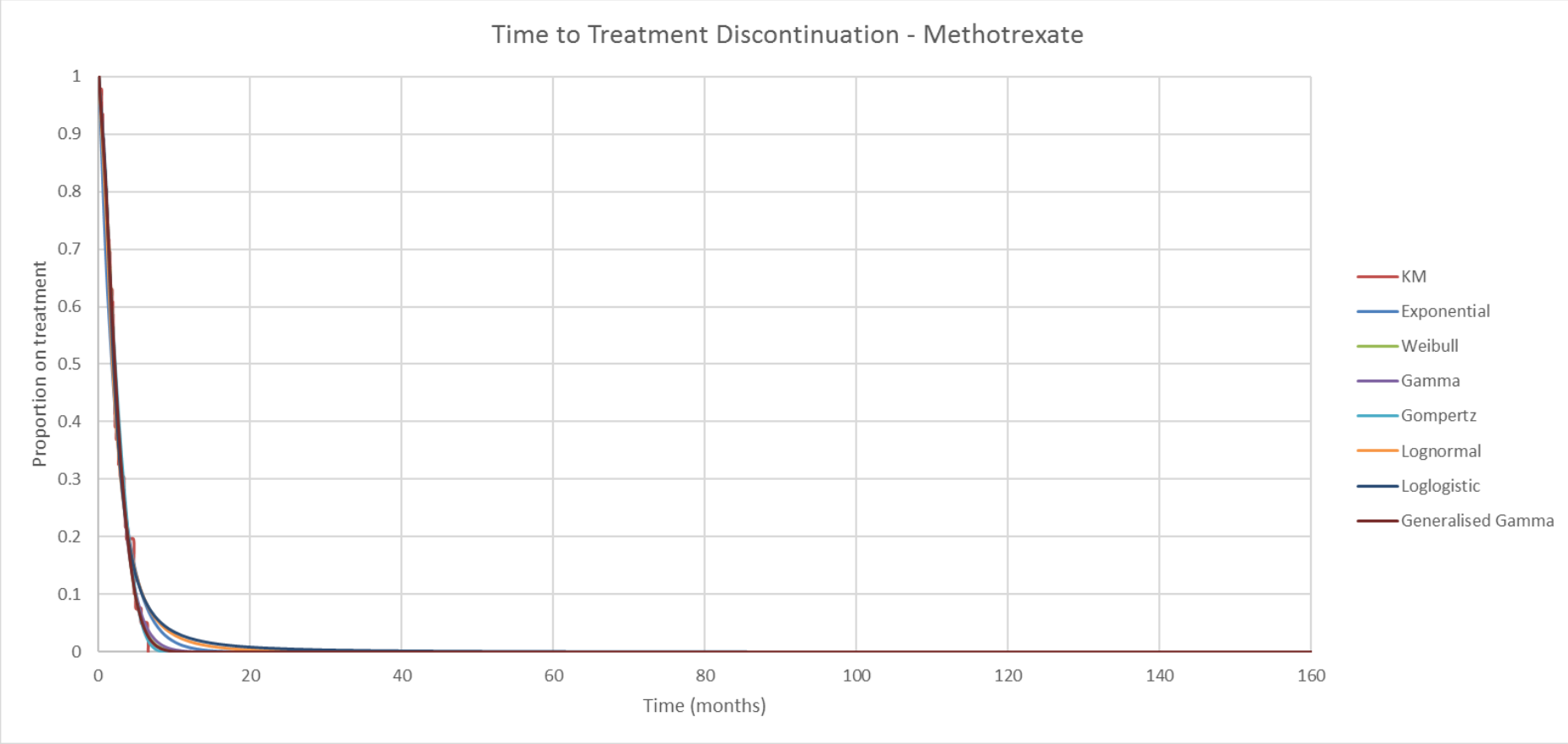
Figure 20: Long-term extrapolation of non-spline models for TTD – methotrexate



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b. Please provide a scenario analysis using docetaxel as 'intended investigator's choice' for the nivolumab comparator and another scenario analysis using methotrexate as 'intended investigator's choice' for the nivolumab comparator.

The results of this scenario analyses are presented in Table 21 (without PAS) and Table 22 (with PAS) below. This scenario analyses are based on the selection of curves as described above in response to Question B2a. Further features of the model informing this analysis are listed in response to Question B2 c, below.

Table 21: Results of scenario analysis exploring differing efficacy of comparator therapies (without PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab (matched with Docetaxel)	[redacted]	1.49	[redacted]				
Docetaxel	13,025	0.76	0.47	[redacted]	0.73	[redacted]	[redacted]
Paclitaxel	13,092	0.76	0.47	[redacted]	0.73	[redacted]	[redacted]
Nivolumab (matched with Methotrexate)	[redacted]	1.23	[redacted]				
Methotrexate	12,211	0.58	0.31	[redacted]	0.65	[redacted]	[redacted]

Table 22: Results of scenario analysis exploring differing efficacy of comparator therapies (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab (matched with Docetaxel)	[redacted]	1.49	[redacted]				
Docetaxel	13,025	0.76	0.47	[redacted]	0.73	[redacted]	£34,286
Paclitaxel	13,092	0.76	0.47	[redacted]	0.73	[redacted]	£34,157
Nivolumab (matched with Methotrexate)	[redacted]	1.23	[redacted]				
Methotrexate	12,211	0.58	0.31	[redacted]	0.65	[redacted]	£33,756

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c. Please provide an updated model including these estimates.

An updated model has been provided along with this response, in which:

- Efficacy of docetaxel (and therefore paclitaxel) and methotrexate is modelled based on treatment-specific estimates from CheckMate-141
- Efficacy of nivolumab is based on matched nivolumab data for the comparisons to docetaxel and methotrexate separately
- All adjustments summarised in response to Question B1 have also been made
- Rates of adverse events are included based on their rates in the individual docetaxel and methotrexate subgroups, and the corresponding matched nivolumab subgroups. Please note that the adverse events included correspond to the same adverse events as included in our original model (i.e. grade 3/4 all-cause adverse events that occurred in ≥5% of patients in the intention-to-treat population of CheckMate-141, plus further adverse events suggested as relevant by clinical opinion); only the rates of these adverse events has been adjusted to the treatment-specific rates. This approach has been taken because reapplying the ≥5% criterion to the treatment-specific groups was considered inappropriate; due to the small size of the subgroups of patients who received methotrexate or docetaxel, a very small absolute frequency of an adverse event can very easily represent ≥5% occurrence. A list of all of the adverse events that would meet the criteria for inclusion if reapplying this rule to the individual methotrexate and docetaxel subpopulations or the nivolumab population is provided in Table 23 for transparency (this table also includes the rates of the adverse events included as a result of clinical opinion, and which may therefore not reach the 5% threshold across any group). However, for the reason outlined above, it was considered most appropriate to still apply the criterion for adverse event inclusion to the ITT population and then incorporate the rates of included adverse events based on treatment-specific estimates. This is supported by clinical opinion which, upon reviewing the final list of adverse events in the original model, indicated that no adverse events of relevance had been missed.
- Treatment-specific health-state utilities (i.e. individual utilities for methotrexate and docetaxel) have been applied for comparator therapies, as opposed to using the "investigator's choice" utility that was applied in our original model

Table 23: All-cause Grade 3-4 adverse events that occurred in ≥5% of patients treated with either nivolumab, docetaxel or methotrexate in CheckMate 141 (all-treated population)

Adverse event, n (%)	Nivolumab (n=236)	Methotrexate (n=46)	Docetaxel (n=52)
Alopecia	0	0	3 (5.8)
Anaemia	14 (5.9)	4 (8.7)	5 (9.6)
Anorexia*	3 (1.3)	1 (2.2)	2 (3.8)
Asthenia	5 (2.1)	0	3 (5.8)
Diarrhoea	2 (0.8)	0	3 (5.8)
Dysphagia	9 (3.8)	1 (2.2)	1 (1.9)
Dyspnoea	13 (5.5)	2 (4.3)	0
Fatigue	8 (3.4)	3 (6.5)	4 (7.7)

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Hyperglycaemia	3 (1.3)	0	3 (5.8)
Hyponatraemia	11 (4.7)	4 (8.7)	5 (9.6)
Leukopenia	1 (0.4)	0	3 (5.8)
Lymphocyte count decrease	3 (1.3)	1 (2.2)	3 (5.8)
Nausea and vomiting	2 (0.8)	1 (2.2)	0
Neutropenia	0	3 (6.5)	5 (9.6)
Pleural effusions	2 (0.8)	1 (2.2)	4 (7.7)

Includes events reported between the first dose and 30 days after the last dose of study therapy.
*Reported as decreased appetite
Shaded adverse events represent those included based on clinical opinion rather than meeting the criterion for trial-based adverse events

B3. **Priority:** In the CS, equivalent effectiveness of docetaxel and paclitaxel is assumed.[1] This assumption is justified in the CS by two references. However, the ERG could not find any trial evidence in these references to support the assumption of equivalent effectiveness of docetaxel and paclitaxel. Indeed, one reference seems to indicate that docetaxel is inferior to paclitaxel at least in combination with platinum-based therapies: 'Regimens with carboplatin and paclitaxel did not seem to be much different from regimens with cisplatin and paclitaxel. However, a recently reported phase II trial in R/M-SCCHN (including patients with Eastern Cooperative Oncology Group (ECOG) grade 0–2) conducted by the Southwest Oncology Group indicated only moderate activity of carboplatin plus docetaxel.' (p. vii254)

a. Please provide specific information from these references or other sources to justify the assumption of equivalent effectiveness of docetaxel and paclitaxel.

The clinical systematic review conducted as part of the CS identified no head-to-head trials that investigated the efficacy of docetaxel versus paclitaxel (see Question A9 for more details of the paclitaxel trials identified). In the absence of any definitive clinical data, an assumption of equivalence between docetaxel and paclitaxel, in terms of OS specifically, was presented in the CS, based on clinician feedback:

"… *clinical expert opinion suggests that there is no difference in efficacy in terms of OS between the comparators listed in the final scope for this appraisal (docetaxel, paclitaxel and methotrexate)*.[6,7]"

where 6 and 7 refer to an international advisory board and feedback from two UK clinical experts, respectively.[22, 23] Opinion from the clinicians consulted at the international advisory board was that the therapies included in the IC arm of CheckMate 141 (docetaxel, methotrexate and cetuximab) are expected to be associated with similar OS, assuming patient profiles are similar – this discussion was focussed on the CheckMate 141 trial and so paclitaxel was not considered here.[22] The two UK clinical experts, who were consulted independently from one another, both

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described a lack of definitive clinical data to suggest that either docetaxel or paclitaxel was better than the other, with one clinical expert noting that there is no perceived difference in efficacy between the two therapies.[23]

The equivalence of docetaxel and paclitaxel was reiterated in the CS when describing the comparators included in the cost-effectiveness model:

"*Docetaxel and paclitaxel are both taxanes and are often grouped together in discussion of clinical agents for the treatment of R/M SCCHN; an assumption of clinical equivalence is therefore considered appropriate and is supported by UK clinical opinion.*[4,7]"

where 4 refers to the review article by Vermorken *et al*. (2010).[24] This article was referenced to support the first phrase of the sentence above, and refers to paclitaxel and docetaxel together as "the taxanes" when describing the use of single-agent chemotherapy for the treatment of R/M SCCHN:

"Several new active agents (defined as inducing responses in ≥15% of cases) have been introduced more recently, such as… and the taxanes paclitaxel and docetaxel. The taxanes are among the highest scoring agents, with response rates varying between 20% and 43%, illustrating the earlier mentioned variability in patient and tumour characteristics."[24]

No further detail is provided in this reference as to the relative efficacy of paclitaxel and docetaxel as single agents. The trials cited in the question above investigated the use of combination chemotherapies (a taxane plus platinum-based therapy) and so their relevance to this appraisal may be questioned (combination therapies were not included in the systematic review, for example). In any case, these trials do not provide direct evidence of relative efficacy between combination therapies that include either docetaxel or paclitaxel and a naïve comparison between these trials is not considered appropriate. Furthermore, the phase II trial referred to in the question was a single-arm, non-controlled trial from which very limited conclusions can be made as to the relative efficacy of this docetaxel-carboplatin regimen.[25]

B4. For the time-to-event models for PFS and TTD, the company used generalised-gamma and log-logistic distributions respectively.

a. Please justify why the generalised-gamma distribution was used for PFS, because 1) the log-logistic distribution had a better statistical fit and 2) no plausible argument to deviate from this distribution was mentioned in the CS. [1] Note that the argument of visual inspection of fit with the Kaplan-Meier curve does not seem credible as this is inconsistent with the AIC/BIC.

The choice of the generalised-gamma distribution in the base case was based on the reasoning outlined in our submission document; that is, that a visual inspection of the curves seemed to suggest that the generalised gamma curve had a more similar shape to the Kaplan-Meier data than the loglogistic curve. The NICE Decision Support Unit Technical Support Document notes

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that is "is often useful to assess how well a parametric survival model fits the clinical trial data by considering how closely it follows the Kaplan Meier visually" and in an effort to adhere to this well-established guidance document we were keen to therefore consider this approach as part of the decision-making process. Visual inspection does favour the generalised-gamma distribution over the loglogistic in that, for the nivolumab arm in particular, where there are large differences between the Kaplan-Meier curve and the parametric distribution, the size of these differences is notably greater when looking at the loglogistic curve versus the generalised-gamma curve. Furthermore, the portion of the Kaplan-Meier curve where visual inspection indicated a better fit for the loglogistic curve is the tail end of the Kaplan-Meier plot; at this point there were few patients left in the analysis and hence in considering the choice of distribution we prioritised visual fit to earlier sections of the Kaplan-Meier curve where the Kaplan-Meier curve is informed by a greater number of patients.

Nevertheless, we agree that AIC values present a considerably more robust methodology for assessing statistical fit and acknowledge that the AIC values favour the loglogistic curve as opposed to the generalised-gamma. We note however that the differences in AIC between these two curves for the IC arm are negligible, but that the AIC values for the nivolumab arm do favour the generalised-gamma.

It is important, however, to place this discussion in the context of the importance of the selection of the PFS distribution for determining ultimate cost-effectiveness. As such, Table 24 provides deterministic base case results from our original submitted model (at list price) using a generalised-gamma curve for PFS (i.e. the results as presented on page 148 of our original submission) alongside equivalent results with this analysis re-run using the loglogistic distribution as the choice of curve for PFS. As can be seen, the choice of a loglogistic curve for PFS has little impact on the ICERs for nivolumab versus IC.

Table 24: Summary of base case results from originally submitted model under different choice of PFS curves (without PAS)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Deterministic base case results (list price) using a generalised gamma choice for PFS							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Deterministic base case results (list price) using a loglogistic choice for PFS							
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,556	0.65	0.38	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,621	0.65	0.38	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,553	0.65	0.38	[redacted]	0.68	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

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b. Please justify why the log-logistic distribution was used for TTD and not the generalised-gamma distribution. The statement in CS section 5.3.4.1 regarding slightly better statistical fit for both nivolumab and IC is incorrect, as the generalised-gamma distribution provides the best statistical fit (according to the Akaike information criterion (AIC) in CS Table 34).

Whilst it is the case that AIC is lower for the generalised-gamma distribution than the loglogistic distribution for IC of therapy, in considering goodness-of-fit to the nivolumab arm of the model, the AIC value is actually lower for the loglogistic distribution than the generalised gamma distribution (Table 33 of our submission). In both arms of the model the difference in AIC between the two distributions was very (and similarly) small. In this context, priority for goodness-of-fit was given to the nivolumab arm since TTD with nivolumab is a far greater driver of cost-effectiveness results than TTD of comparators. Finally, it should be noted that the BIC values are lower for the loglogistic distribution than the generalised-gamma distribution in both the nivolumab and IC arms of the model, therefore favouring the selection of the loglogistic curve.

Adverse events

B5. The impact of AEs on health related quality of life and costs is incorporated only at the first cycle in the economic model.

a. Please provide a justification for this approach.

This approach to incorporating the impact of AEs is a pragmatic one consistent with that which has been used in prior appraisals of nivolumab. Modelling the occurrence of adverse events over time would either require direct reflection of the timing of occurrence of adverse events based on patient-level data or assumption of a constant per cycle rate of occurrence of adverse events based on probabilities of selected adverse events over a defined time-period. Whilst both approaches may be feasible, they would introduce additional complexity into the model. In our model, the contribution of adverse event-related costs and utilities to total QALYs and costs in each model arm and also to incremental QALYs (2%) and costs (1% versus all comparators) is very small. As such, this additional complexity was not considered to be warranted.

Furthermore, the major limitation of the approach taken to modelling of adverse events is that it does not take into account the impact of discounting on disutilities and costs that occur in later model cycles. However, this has the impact of overestimating the contribution of adverse events to total costs and total QALYs in each arm of the model. Altering the approach to model adverse events over time would result in a decrease in adverse event-related costs and disutilities in each of the model arms. Although the precise impact on the incremental costs and utilities of nivolumab versus the comparators is unknown, this would further diminish the contribution of adverse events to total costs and QALYs in each model arm. The scenario analysis presented in Table 76 and Table 77 of our submission in which adverse event disutilities were set to zero highlights the minimal impact of adverse events utilities on cost-effectiveness results.

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b. Please provide a scenario analysis incorporating the impact of AE on health related quality of life and costs over time.

For the reasons outlined above, and in the interest of prioritising other requests given the limited time to respond to the clarification questions, this scenario analysis has not been provided.

c. Please provide an updated model including these estimates.

Please see our response above to Question B5b.

B6. CS Table 21 shows treatment-related 'select' AEs from the CheckMate 141 trial with a potential immunological cause that are of special clinical interest with the use of nivolumab. These AEs with a potential immunological cause were analysed according to organ category (skin, gastrointestinal, endocrine, pulmonary, hepatic, and renal)[1] but were not incorporated in the economic model.

a. Please provide a cost-effectiveness scenario including treatment-related 'select' AEs reported in CS Table 21.

In response to this clarification question we have revisited the frequencies of 'select' AEs of any cause that occurred in the CheckMate-141 trial. The rates of these AEs in the nivolumab and IC arms of the model are provided in document (Supplementary 2, commercial in confidence) accompanying this submission. As can be seen, these 'select' adverse events were rare in both the nivolumab and IC arms of the CheckMate-141 trial.

Based on these very low frequencies of occurrence (which are in all cases well below the 5% criterion for selection of grade 3-4 adverse events applied in our model), we feel that justification for inclusion of these adverse events is limited. Furthermore, following pragmatic searches we have been unable to identify costs or utility values for any of these 'select' adverse events (with one exception) and note that none of these 'select' adverse events (bar one) has been included in prior/ongoing appraisals of nivolumab by NICE in other indications. The exception to this is pneumonitis, which was included in the appraisal of nivolumab in metastatic renal cell carcinoma (ID853). The rates of pneumonitis are reported previously in the supplied reference and the cost and disutility associated with this adverse event is provided in Table 25.

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Table 25: Cost and utility decrement for pneumonitis episode

Grade III/IV pneumonitis	Value	Source
Cost per episode	£418.91	Bronchoscopy (19 years and over): £316, regular day and night admissions (DZ69A) NHS reference costs 2014-2015 Weekly OP appointments with a GP: 11.7 minutes of patient contact, excluding direct staff costs and without qualifications £33. Average across both arms is 2.93 weeks = £96.53 per episode (PSSRU 2015) Four weeks of steroids: Fluticasone propionate, 50 microgram per inhalation, 60 inhalations=£6.38 (based on 100mg (i.e. 2 inhalations) per day for 30 days) (MIMS, http://www.mims.co.uk/drugs/respiratory-system/asthma-copd/flixotide-evohaler)
Utility decrement	-0.15	Clinical validation of TA215 estimates

Therefore, having reviewed the available information on the rates of occurrence of 'select' adverse events and their associated disutilities and costs, it is only feasible to update the model to include pneumonitis. A scenario analysis in which pneumonitis is added as an adverse event to the revised base case described in Question B1 provides the cost-effectiveness results presented below in Table 26 (without PAS) and Table 27 (with PAS).

Table 26: Results of scenario analysis including pneumonitis (without PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]

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Table 27: Results of scenario analysis including pneumonitis (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£35,044
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,919
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£35,050

b. Please provide an updated model including these estimates.

The revised base case model incorporates the functionality to run this scenario analysis.

Health related quality of life

B7. **Priority:** In the CS, the utility is estimated based on the CheckMate 141 trial using the EQ-5D-3L questionnaire.[1] However, data for both EQ-5D-3L and tumour response in [redacted] of 361 patients ([redacted]%) were completely missing (i.e. unable to calculate a utility score at any time point).

A copy of Table 38 from our original submission, in which EQ-5D data is missing for [redacted]/361 patients, is provided below (Table 45).

Table 28: Original CS Table 38

Health state	Nivolumab		IC of therapy		Overall	
	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Having reconsidered this data, a further [redacted] patients have been identified who had a baseline EQ-5D value but were not assigned to a health state at baseline and were therefore not included in the above analysis. Therefore, the above calculation of utility values by therapy and by health state has been repeated but including these [redacted] patients by assuming in all cases that their health state at baseline was progression-free. This is considered a reasonable assumption given the CheckMate-141 eligibility criteria. Table 29 presents the results of the recalculation of the utility values including these patients. Therefore, in these analyses there are a remaining [redacted]/361 patients with missing data.

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Table 29: Updated equivalent to Table 38 with additional baseline EQ-5D assessments allocated as pre-progression

Health state	Nivolumab		IC of therapy		Overall	
	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As would be expected, there is no change to the progressed disease utilities in this revised analysis. The progression-free utilities are seen to be slightly lower for both nivolumab and IC, and for the overall analysis.

A scenario analysis in which the revised base case is adjusted to incorporate the treatment-specific health-state utility values presented in Table 29 as opposed to the original treatment-specific utilities from Table 28 has been conducted, the results of which are presented below.

Table 30: Results of scenario analysis using Table 29 utility values (without PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]

Table 31: Results of scenario analysis using Table 46 utility values (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£35,371
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£35,245
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£35,377

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a. Please compare patient characteristics of patients which were included and patients excluded from utility values calculations for both treatment groups separately and for the whole trial population combined (independent of treatment groups).

Patient characteristics for patients included and excluded from utility calculations are provided in Appendix i. These have been provided both considering the original population of included/excluded patients (i.e. [redacted] excluded patients - Table 28) and the updated population of included/excluded patients (i.e. [redacted] excluded patients - Table 29)

The tables provided in Appendix i are as follows:

- Table 6.1.1 summarises characteristics for patients in the current Table 28
- Table 6.1.2 summarises the patients missing from Table 28
- Table 6.1.3 summarises the patients in the updated Table 29
- Table 6.1.4 summarises the patients missing from Table 29

b. Please clarify what the likely causes of missing data were and what the potential impact of these missing data on the estimation of the utility scores would be, separately for patients who had completely and partially missing utility data.

A summary of missing data patterns for the EQ-5D questionnaire is provided in Table 32. A high proportion of patients dropped out of the assessments before week 27. This table also provides information on the number of deaths and cases of disease progression, as two key potential reasons for patient dropout.

A high proportion of missing data from 45 weeks are due to deaths. Patients who progressed may have gone on to have the planned additional follow ups but this may also be a reason for missing data. Other reasons for missing data were not collected in the study. Graphs grouping patients by the timing of their last assessment (not shown) do not show any clear trend for a bias towards either treatment group.

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Table 32: Missing data patterns

Number of EQ-5D-3L utility index (UK weights) Assessments by Visit (N=347)				
Analysis Visit	**Number of missing**	**Cumulative Number of deaths**	**Cumulative Number of disease progressions**	**Cumulative Number of deaths & disease progressions**
0	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]
39	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]
51	[redacted]	[redacted]	[redacted]	[redacted]
57	[redacted]	[redacted]	[redacted]	[redacted]
63	[redacted]	[redacted]	[redacted]	[redacted]
69	[redacted]	[redacted]	[redacted]	[redacted]

c. Please recalculate the figures reported in CS Table 38 while imputing missing values (for the patients with completely missing utility data and patients with partially missing utility data) using multiple imputation (incorporating potential explanatory variables and using at least 10 imputations).

   i. Please provide in detail, the methods used to impute and pool the utility data.

   ii. Please provide a scenario analysis using these newly calculated utility values

   iii. Please provide an updated model containing these updated utility values

Imputation Methods

Multiple imputation was carried out using PROC MI in SAS version 9.4. The MCMC method was used to deal with non-monotone missing data patterns. For each model, patients who had a baseline EQ-5D score that was not originally included in Table 28 (as there was no response assessment assigned) were allocated to the pre-progression health state since at the point of randomisation all patients should be pre-progression. In other words, the imputation was

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performed on the patients that informed the utility estimates given in Table 29 rather than the patients that informed our original utility analysis.

Imputing was performed by pooling over time. Patients' mean EQ-5D index across their pre-progression time points and across their post-progression time points were calculated and then any missing values imputed. The imputation model used age group, ECOG performance status, smoking status and prior chemotherapy as the explanatory variables. The imputation was run (10 imputations) without including treatment arm in the imputation model and then repeated by treatment arm. PROC MIANALYZE was used to pool the imputations and estimate means and standard errors.

The results of the utility analysis using the imputation method described above are presented in Table 33 (for the IC arm) and Table 34 (for the nivolumab arm).

These results should be heavily caveated. Model-based and stochastic imputation procedures offer advantages over less sophisticated methods (e.g., mean imputation, last observation carried forward) in that they can yield accurate projections assuming that missingness is explained fully by observed data and can facilitate more conservative inferences than procedures treating imputations as real. However, they are not a panacea.

The method employed to impute missing utility data (i.e., Markov Chain Monte Carlo) as implemented in the widely used SAS procedure PROC MI assumes that all variables share a joint multivariate normal distribution. While imputations generated for this response appeared to preserve variable distributions, the assumption of normality when working with utility data is overly restrictive, and the impact of using more flexible imputation procedures (e.g., imputation by chained equations) could not be explored due to the time constraint. The method of imputing mean utility values pre- and post-progression made best use of the available data and allowed BMS to provide the requested information. While there was potential for the introduction of bias due to aggregation, the model-based imputation of missing values at individual assessment time points was deemed infeasible due to the proportion of missing data later in follow up. Moreover, the imputation of utilities directly, as opposed to individual EQ-5D item responses, could have been a source of potential bias. Given available data and limited time, the process of imputation was necessarily simplified to ensure that the request for information could be satisfied.

Lastly, it is important to acknowledge that model-based imputation procedures can fail if the process for data missingness is not random. Given the absence of a test for missing at random vs. not at random, it is impossible to say with certainty that the imputations generated for this response were free of bias. The models used to facilitate imputation were specified carefully and with input from BMS clinical and health economic experts. However, limitations of the data were felt clearly. Most notably, the absence of time-varying measures of changes in clinical status could explain differences in the magnitude of mean utilities estimated from available cases vs. all cases with missing data imputed.

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Unfortunately, there exists no Technical Support Document available regarding the most appropriate methods for undertaking and exploring the imputation of missing utility values, which was also a limitation of the required analysis.

In addition to the above considerations, whilst the utility values presented in our original submission were validated with clinicians, there has been no opportunity to perform any exercise to determine the clinical validity of the utility values reported in the two tables below.

Given this, and the aforementioned concerns, BMS believes that the most appropriate utility values to utilize in the base case of the cost-effectiveness model are those provided in Table 29.

Table 33: Imputation (pooled visits) – including arm in the imputation model – IC arm

Parameter Estimates (10 Imputations)							
Parameter	**Estimate**	**Std Error**	**95% Confidence Limits**		**DF**	**Minimum**	**Maximum**
pre_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pd_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 34: Imputation (pooled visits) – including arm in the imputation model – Nivolumab arm

Parameter Estimates (10 Imputations)							
Parameter	**Estimate**	**Std Error**	**95% Confidence Limits**		**DF**	**Minimum**	**Maximum**
pre_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pd_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Although the imputed utility values have not undergone any formal validation process, an exploratory scenario analysis has been conducted to determine their impact on the cost-effectiveness results. The results of this analysis both with and without the PAS are presented in Table 35 and Table 36, respectively, below.

Table 35: Results of scenario analysis using imputed utility values (without PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	[redacted]

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Table 36: Results of scenario analysis using imputed utility values (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	12,538	0.65	0.37	[redacted]	0.68	[redacted]	£40,985
Paclitaxel	12,603	0.65	0.37	[redacted]	0.68	[redacted]	£40,839
Methotrexate	12,535	0.65	0.37	[redacted]	0.68	[redacted]	£40,992

d. Please provide the Table requested above (CS Table 38 while imputing missing values, question B6c) stratified for patients being on treatment (nivolumab or IC) or not.

Utility values by health state and stratified by on/off treatment arm for the two arms of the CheckMate-141 trial are provided below.

Table 37: Utility values stratified by treatment status - IC

Parameter Estimates (10 Imputations)							
Parameter	Estimate	Std Error	95% Confidence Limits		DF	Minimum	Maximum
preon_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
preoff_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pdon_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pdoff_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 38: Utility values stratified by treatment status - nivolumab

Parameter Estimates (10 Imputations)							
Parameter	Estimate	Std Error	95% Confidence Limits		DF	Minimum	Maximum
preon_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
preoff_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pdon_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pdoff_mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

e. Please provide the imputed utility values for every measurement occasion in the trial (including mean, number of observations, and standard deviation (SD)), stratified by treatment (nivolumab or IC), for:

   i. Pre-progression

   ii. Post-progression

   iii. On treatment (i.e. on nivolumab or IC)

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iv. Off treatment (i.e. off nivolumab and IC)

For this longitudinal analysis, a staged approach to imputation was used as detailed in "Design and Analysis of Quality of Life Studies in Clinical Trials" Diane Fairclough, 2002.[26] Missing baseline EQ-5D scores were imputed first using baseline covariate data (age group, ECOG performance status, smoking status and prior chemotherapy) as the explanatory variables. Arm was not used in this initial imputation at baseline as the trial was randomised. Ten sets of imputed values were generated. Following this initial step, the remaining time points were imputed once on each of these initial 10 imputation datasets including the baseline EQ-5D index value, pre/post progression status, log of time to death and arm as the explanatory variables for the imputation.

Initially the imputation was attempted for all time points to week 69. Post progression follow ups were included using time windows to allocate them to the appropriate study week. The imputation model would not converge when including time points past week 15. The level of missing data at these points is very high, therefore this particular model had to be restricted to only baseline, week 9 and week 15 data. Following imputation, any time points past the date of death were deleted as deaths are being treated as a separate health state in the economic model. The ten imputed values were then pooled using the mean value.

Results from this model are provided below by progression status for the two arms. Please note, however, that only data to week 15 could be included in these summary tables due to convergence issues. Note that due to the restrictions in the number of time points that could be included, the sample size for the progressive disease state is very small. Therefore, this method of imputation should be considered unsuccessful. Based on this, further analysis by on/off treatment for parts iii and iv was not conducted and the below results should not be utilised further.

Table 39: Imputed utility values by measurement occasion

Pooled across 10 imputations			Randomised group							
			INVESTIGATOR CHOICE				NIVOLUMAB 3 mg/kg			
			0	9	15	Overall	0	9	15	Overall
	PD	Mean	[redacted]							
		95_LCLM								
		95_UCLM								
		SD								
		Max								
		Min								
		N								
	pre	Mean								
		95_LCLM								
		95_UCLM								

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Pooled across 10 imputations			Randomised group							
			INVESTIGATOR CHOICE				NIVOLUMAB 3 mg/kg			
			0	9	15	Overall	0	9	15	Overall
		SD	[redacted]							
		Max	[redacted]							
		Min	[redacted]							
		N	[redacted]							

f. Please provide the utility data requested above (question B7e) using the dataset without imputation.

Utility data without imputation and by measurement time point are provided in the various tables below. Table 40 to Table 41 provide analyses based on the original population (i.e. the population corresponding to Table 28). Table 42 and Table 43 provide equivalent results for the population in which it was assumed that patients with missing health status at baseline were progression-free (i.e. the population corresponding to Table 29). The latter set of tables, making the updated assumption in order to increase the population size, are likely to be considered the most relevant.

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Table 40: Utility values with no imputation – by visit, and by progression status

	INVESTIGATOR CHOICE										NIVOLUMAB 3 mg/kg									
	PD					SD/PR/CR					PD					SD/PR/CR				
	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N
0	[redacted]																			
9	[redacted]																			
15	[redacted]																			
21	[redacted]																			
27	[redacted]																			
33	[redacted]																			
39	[redacted]																			
45	[redacted]																			
51	[redacted]																			
57	[redacted]																			
69	[redacted]																			
201	[redacted]																			
202	[redacted]																			
301	[redacted]																			
302	[redacted]																			
303	[redacted]																			
304	[redacted]																			

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Table 41: Utility values with no imputation – by visit, and progression status, with follow-up visits placed in appropriate time window

	INVESTIGATOR CHOICE										NIVOLUMAB 3 mg/kg									
	PD					SD/PR/CR					PD					SD/PR/CR				
	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N
0	[redacted]																			
9	[redacted]																			
15	[redacted]																			
21	[redacted]																			
27	[redacted]																			
33	[redacted]																			
39	[redacted]																			
45	[redacted]																			
51	[redacted]																			
57	[redacted]																			
63	[redacted]																			
69	[redacted]																			

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Table 42: Utility values with no imputation (using progression-free at baseline assumption) – by visit, and progression status

	INVESTIGATOR CHOICE										NIVOLUMAB 3 mg/kg									
	PD					SD/PR/CR					PD					SD/PR/CR				
	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N
0	[redacted]																			
9	[redacted]																			
15	[redacted]																			
21	[redacted]																			
27	[redacted]																			
33	[redacted]																			
39	[redacted]																			
45	[redacted]																			
51	[redacted]																			
57	[redacted]																			
69	[redacted]																			
201	[redacted]																			
202	[redacted]																			
301	[redacted]																			
302	[redacted]																			
303	[redacted]																			
304	[redacted]																			

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Table 43: Utility values with no imputation (using progression-free at baseline assumption) – by visit, and by progression status, with follow-up visits placed in appropriate time window

	INVESTIGATOR CHOICE										NIVOLUMAB 3 mg/kg									
	PD					SD/PR/CR					PD					SD/PR/CR				
	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N	Mean	SD	Max	Min	N
0	[redacted]																			
9	[redacted]																			
15	[redacted]																			
21	[redacted]																			
27	[redacted]																			
33	[redacted]																			
39	[redacted]																			
45	[redacted]																			
51	[redacted]																			
57	[redacted]																			
63	[redacted]																			
69	[redacted]																			

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g. Please justify why each EQ-5D-3L measurement was assumed to be independent while some patients had multiple EQ-5D-3L measurements and clarify what the expected impact of this method is on the results (i.e. why the company believes this would not bias the results).

There is a lack of clear guidance from NICE on the topic of capturing independence or not of utility measurements where patients have multiple measurements. By including all questionnaires this, particularly for PFS, incorporates (at a simplistic level) information on time to response and duration of response for patients, which may differ between treatment arms.

Within our original submission, we presented an analysis of utility values for patients in the progression-free health state up to Week 21 of the analysis (Table 40 in the original CS). The utility values derived from this analysis were seen to be similar to those for the analysis at all time points (Table 38 in the original CS). Due to its earlier cut-off, the analysis up to Week 21 represents an analysis that is less contaminated by multiple measurements per patient. The similarity of the utility values derived from these analyses therefore provides some indirect support that the impact of multiple non-independent measurements does not unduly influence the resultant utility values.

Finally, within our original submission we presented a scenario analysis (Scenario 12) in which health state utility values for the overall trial population, rather than treatment-specific utility values, were used. Therefore, in this scenario analysis no differences in health state utility between nivolumab and comparators were assumed. Therefore, should any bias introduced by the incorporation of multiple measurements be in favour of nivolumab, this scenario analysis provides an indication of the potential influence on the ICER, down to the level of equal utility between the two treatments. This scenario analysis resulted in an increase to the modelled ICER, though the “with PSA” ICER was still considerably below the cost-effectiveness threshold assuming end-of-life criteria.

Resource use and costs

B8. In the CS, the proportion of patients receiving subsequent treatments is based on clinical trial data in the base case and thus assumed to be dependent on the initial treatment (see CS Table 46).[1]

a. Please justify why the proportion of patients receiving subsequent treatments is dependent on the initial treatment instead of being assumed to be equal for all comparators.

In the base case analysis, the proportion of patients receiving subsequent systemic therapy was based on data from CheckMate 141. These proportions were similar between treatment arms (nivolumab, 29.6% and IC, 32.2%).[3] Scenario analyses were also conducted in which the proportion of patients receiving subsequent systemic therapy was assumed to be equal (12%,

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based on market research data) (Scenario 17) and in which the cost of subsequent therapy was removed from the analysis (Scenario 18).

b. Please justify why the costs of subsequent treatments are assumed to be independent of the initial treatment, which is inconsistent with the differential proportion of patients receiving subsequent treatments. This is also inconsistent with the fact that many more patients in the nivolumab arm received 'experimental drugs'.

The choice (and therefore cost) of subsequent systemic therapy was not based on data from CheckMate 141 and was instead based on assumptions related to what would be expected in clinical practice, e.g., patients who had received either docetaxel or paclitaxel as the initial treatment were assumed not to be treated with another taxane and were thus all assumed to receive methotrexate.

The rationale for taking this approach has already been described in the CS on page 136 and is also provided below:

"In CheckMate 141, a variety of subsequent therapies, including investigational therapies, were received by patients in addition to those listed below (see Appendix 3 for full details). For simplicity and applicability, the model restricts the choice of post-discontinuation therapies to those which would be expected to be used in current UK clinical practice (i.e. docetaxel and methotrexate). The dosing and cost of docetaxel and methotrexate were assumed to be the same as when used as an initial therapy (see Section 5.5.2)."

That experimental drugs were used as subsequent therapies in CheckMate 141 precludes the use of trial data in the model as costs for these drugs are not likely to be available.

Finally, as discussed under Question A3, the preliminary assessment that "that many more patients in the nivolumab arm received 'experimental drugs'" is incorrect.

B9. Table 50 refers to previous technology appraisals (TAs) as source for the cost of different adverse events.[1]

a. Please provide full references to the primary sources used in the previous TAs and a digital copy of the primary sources.

The TAs and primary references used to source of costs for AEs are presented in Table 44. These costs were primarily based on NHS reference costs: https://www.gov.uk/government/collections/nhs-reference-costs (accessed: 5th October 2016).

Digital copies of the TAs documents used to source these costs are provided alongside this response document.

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Table 44: Source of adverse event costs

Adverse Event	Cost	NICE TA Reference	Underlying source
Fatigue	£3,110.11	TA347 MS and ID811 MS	2014/15 NHS Reference Costs for weighted average of acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC 0-Score 8+ (SA01G-K)
Dyspnoea	£0	ID811 MS	Clinical opinion
Hyponatraemia	£657.84	ID811 MS	Not referenced
Anaemia	£3,110.11	TA347 MS and ID811 MS	2014/15 NHS Reference Costs for weighted average of acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC 0-Score 8+ (SA01G-K)
Neutropenia	£478.31	TA347 MS and ID811 MS	2014/15 NHS Reference Costs for weighted average of agranulocytosis with CC Score 0-13+ (weighted average)
Dysphagia	£3,305.54	TA172 ERG report	2006/7 NHS Reference Costs for non-elective inpatient weighted average of Complex major Head, Neck or Ear diagnoses with complications (CZ24O-CZ24P)
Nausea and vomiting	£1,324.62	TA172 ERG report	2006/7 NHS Reference Costs for non-elective inpatient weighted average of FC05A & FC05B General Abdominal Disorders with complications
Anorexia	£402.57	TA378 MS	2012/13 NHS Reference costs for weighted average of feeding difficulties and vomiting, with CC Score 0-1+ (PA28A-B)

Abbreviations: MS, manufacturers submission; ERG, Evidence Review Group; TA, technology appraisal.

Sensitivity and scenario analyses

B10. Please justify why a 15% variation around the mean has been implemented in the deterministic and probabilistic sensitivity analyses to calculate the confidence intervals and the SD respectively of several parameters.

In the absence of useful data on the uncertainty associated with model parameters, the application of a set percentage variation is a common approach. Where standard deviations or confidence intervals were available (e.g. for health state utility values) these were applied within the probabilistic sensitivity analysis. However, for a number of parameters, such as cost inputs derived from the British National Formulary or NHS Reference Costs, no measure of variation was available. Therefore, for these parameters a standard percentage variation was applied in the probabilistic sensitivity analysis. This approach has been used in a number of previous models that have been submitted to NICE, including previous models for nivolumab in ID900 (non-squamous lung) and ID811 (squamous lung).[27, 28]

Similarly, for the deterministic sensitivity analysis the approach taken was consistent with previous submissions for nivolumab in other indications. As deterministic sensitivity analysis aims to compare the impact of set changes in individual parameters on model results in order to identify the key model drivers, rather than trying necessarily to reflect empirical uncertainty in model parameters, we considered that applying a consistent proportional variation across parameters (e.g. 15%) was an appropriate method to explore this.

a. Please perform deterministic sensitivity analyses on the parameters of OS, PFS and TTD (implementing parameter uncertainty using the response to question B1).

As requested, the deterministic sensitivity analysis has been performed incorporating the survival model parameters as variables in the analysis. These parameters have been varied by their standard deviations.

The results of the deterministic sensitivity analysis in which survival model parameters are included are presented in the below figures. Please note that these deterministic sensitivity analyses were performed for the revised base case – that is the model as described in response to Question B1.

Figure 21: Tornado diagram of the ten most influential parameters: nivolumab versus docetaxel (without PAS for nivolumab)

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

Figure 22: Tornado diagram of the ten most influential parameters: nivolumab versus paclitaxel (without PAS for nivolumab)

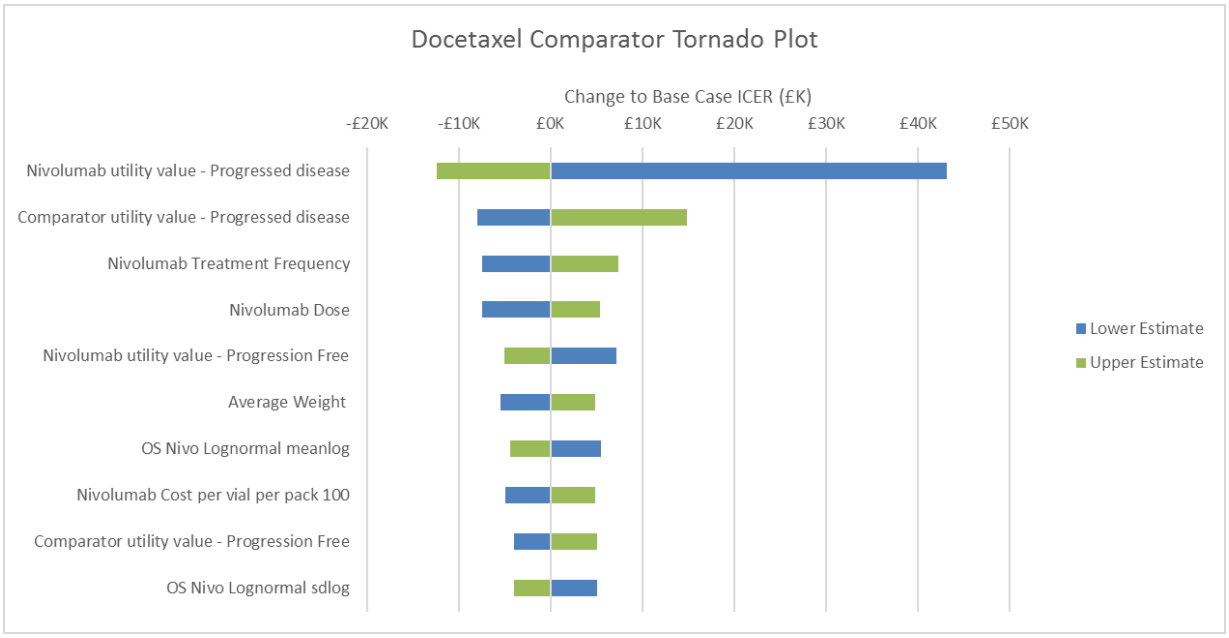
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

Figure 23: Tornado diagram of the ten most influential parameters: nivolumab versus methotrexate (without PAS for nivolumab)

[redacted]

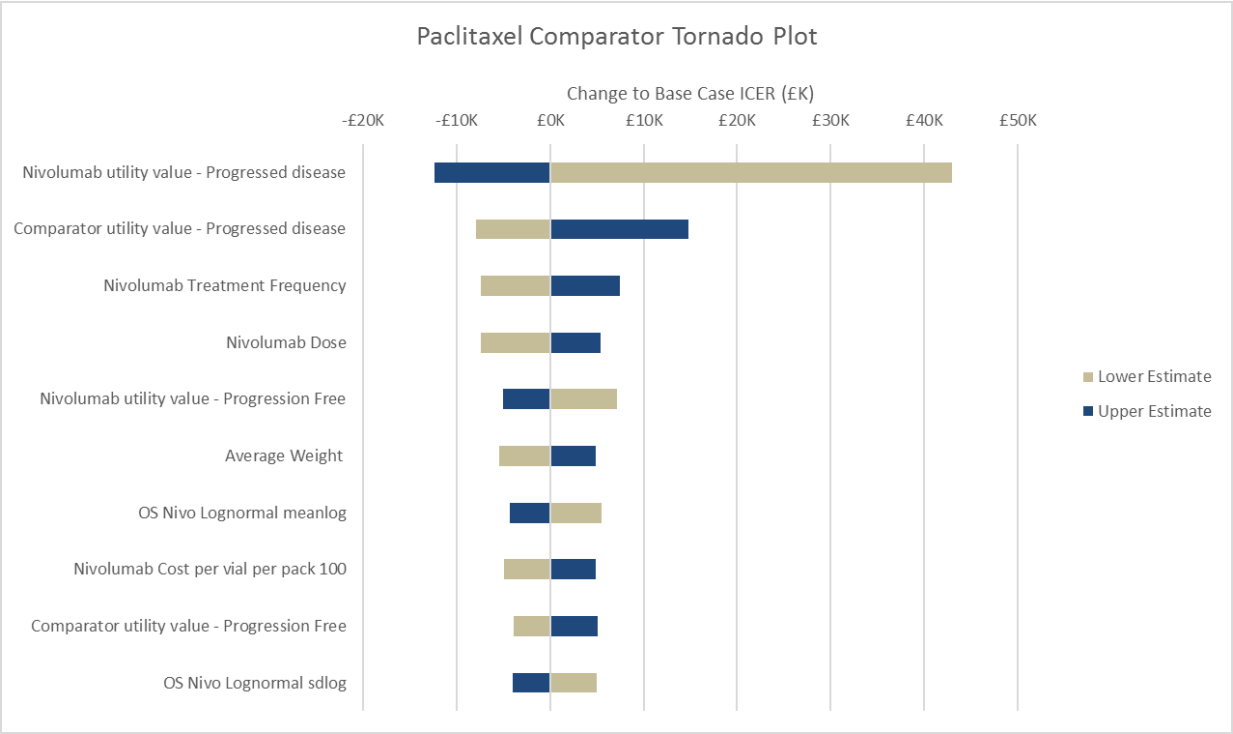
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

Figure 24: Tornado diagram of the ten most influential parameters: nivolumab versus docetaxel (with PAS for nivolumab)



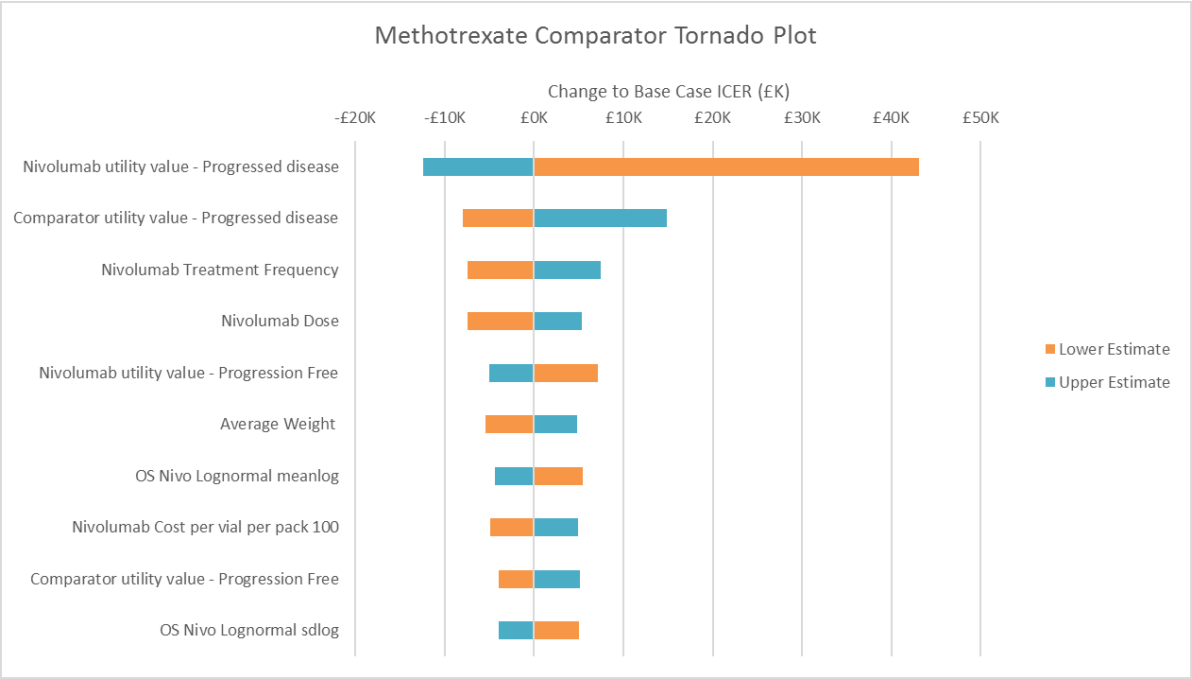
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

Figure 25: Tornado diagram of the ten most influential parameters: nivolumab versus paclitaxel (with PAS for nivolumab)



Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

Figure 26: Tornado diagram of the ten most influential parameters: nivolumab versus methotrexate (with PAS for nivolumab)



Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

b. Please provide the deterministic sensitivity analyses results while incorporating appropriate ranges i.e. use 95% CI based on evidence/empirical data whenever possible.

The deterministic sensitivity analysis results presented in response to part a represent a DSA in which all parameters are varied by their 95% CI or +/- 1 standard deviation in order to incorporate empirical evidence where possible. Where such empirical evidence is not available, parameters are varied by ±20%.

c. Please incorporate appropriate SD estimates in the probabilistic sensitivity analyses i.e. estimated based on evidence/empirical data whenever possible. For example, in case National Health Service reference costs are used, please use lower and upper quartiles in order to incorporate a suitable distribution in the PSA.

The PSA has been adjusted to include standard deviations for model survival parameters and for additional inputs for which these values could be derived. These were available for only a small number of further parameters, including standard deviations for the eMITs drug prices and upper and lower quartiles (from which standard deviations were derived assuming a normal distribution) of some NHS reference costs.

The results of the PSA run using the revised base case model in which these adjustments are incorporated are presented below.

Table 45: Probabilistic results (without PAS for nivolumab)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)
Nivolumab	[redacted]	[redacted]			
Docetaxel	12,470	0.37	[redacted]	[redacted]	[redacted]
Paclitaxel	12,551	0.37	[redacted]	[redacted]	[redacted]
Methotrexate	12,515	0.37	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 46: Probabilistic results (with PAS for nivolumab)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALYs)
Nivolumab	[redacted]	[redacted]			
Docetaxel	12,569	0.37	[redacted]	[redacted]	£34,914
Paclitaxel	12,710	0.37	[redacted]	[redacted]	£34,807
Methotrexate	12,626	0.37	[redacted]	[redacted]	£34,644

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Figure 27: Cost-effectiveness plane: nivolumab (without PAS) versus docetaxel – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 28: Cost-effectiveness plane: nivolumab (without PAS) versus paclitaxel – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 29: Cost-effectiveness plane: nivolumab (without PAS) versus methotrexate – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 30: Cost-effectiveness plane: nivolumab (with PAS) versus docetaxel – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 31: Cost-effectiveness plane: nivolumab (with PAS) versus paclitaxel – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 32: Cost-effectiveness plane: nivolumab (with PAS) versus methotrexate – probabilistic results

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

B11. Please provide a scenario analysis while estimating OS, PFS and TTD based on the EU region subgroup (subgroups as defined for Figures 7.2.1-1 and 7.3.1-1 in the CSR).

This analysis was not considered appropriate in light of the response provided to Question A7 and so has not been conducted. As such, this scenario analysis cannot be provided.

Cost effectiveness results

B12. Please provide disaggregated life-years gained by health states for nivolumab and all comparators (as provided for quality adjusted life-years gained in Table 56 of the CS).[1]

A summary of the life-year gain by health state for nivolumab and comparators in the revised base case model is provided in Table 47.

Table 47: Summary of LY gain by health state – nivolumab versus comparators*

Health state	LY intervention (nivolumab)	LY comparator (IC)	Incremental LYs	Absolute increment	% absolute increment
PF	0.34	0.26	0.09	0.09	13%
PD	0.99	0.39	0.60	0.60	87%
Total	1.33	0.65	0.68	0.68	100%

* Occupancy of health states were based on the IC arm of CheckMate 141 for all comparators.

Abbreviations: IC: investigator's choice; PD: progressive disease; PF: progression-free; LY: life year

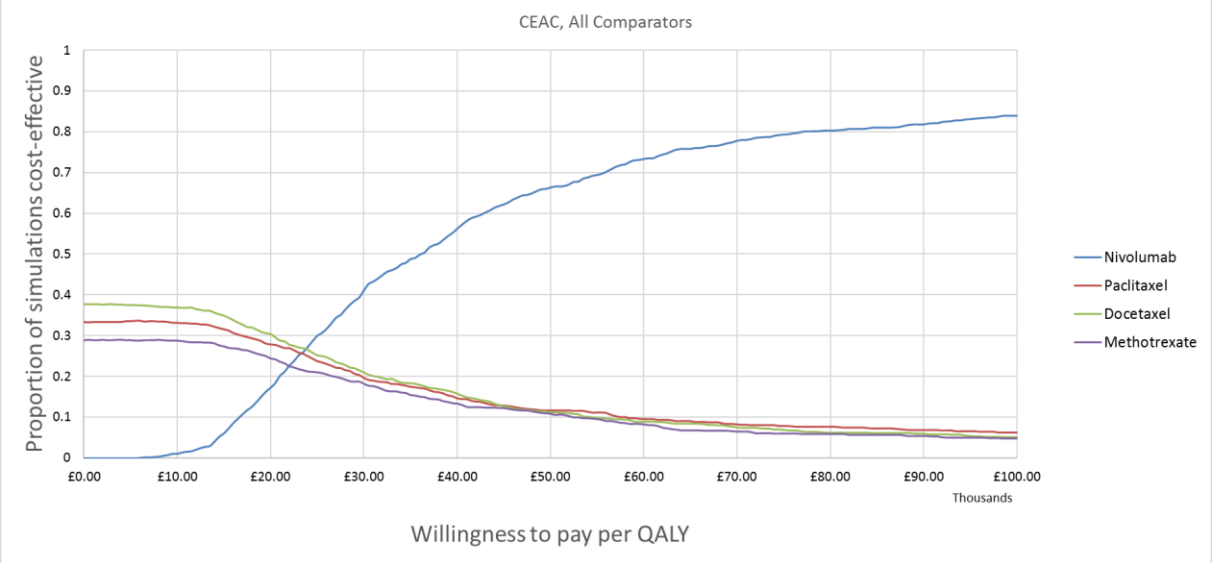
B13. Please provide an updated model which allows for probabilistic analyses of multiple treatments simultaneously.

The cost-effectiveness acceptability curves derived from the PSA run on the revised base case model and incorporating all comparators are provided below for both with PAS and without PAS results.

Figure 33: Cost-effectiveness acceptability curve: all comparators (without PAS)

Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Figure 34: Cost-effectiveness acceptability curve: all comparators (with PAS)



Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Section C: Textual clarifications and additional points

None.

References

1. Bristol-Myers Squibb Pharmaceuticals Ltd. Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]. Company evidence submission: appendices. Single technology appraisal (STA). August 2016.
2. National Institute for Health and Care Excellence (NICE). PMG24: Single technology appraisal: User guide for company evidence submission template (2015). Available: https://www.nice.org.uk/article/pmg24/chapter/Instructions%20for%20companies Accessed: 24th May 2016.
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Appendix i: Demographics of the patients included and not included in Table 38

Table 6.1.1: Demographics for the Patients with data in original Table 38

	Overall (N=258)	Nivolumab (N=176)	Investigator's Choice (N=82)
Region			
US			
European Union			
Rest of World			
Missing			
Age Group			
<65			
65<-<75			
>75			
Missing			
Age (continuous)			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Race			
White			
Black			
Asian			
Other			
Missing			
Number of lines of prior chemotherapy in the metastatic setting			
0			
1			
2			
>3			
Missing			
Baseline ECOG Performance Status			
0			
1			
2			
Unknown			
Missing			
PD-L1 Status			
Positive			
Negative			
Indeterminate			
Missing			
HPV Status			
Positive			

	Overall (N=258)	Nivolumab (N=176)	Investigator's Choice (N=82)
Negative	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Full dataset contained 347 patients not 361
PROGRAM: I:\LOCAL\UK\Staff Folder\TEJUS DESAI\SAS Training\SAS QC Libraries\BS7006A\BS7006A-Demos v0_1.sas
EXECUTED: October 3, 2016 at 08:29 by td

Table 6.1.1 (cont.): Demographics for the Patients with data in original Table 38

	Overall (N=258)	Nivolumab (N=176)	Investigator's Choice (N=82)
American Joint Committee on Cancer stage at study entry			
III			
IV			
Missing			
Time from initial disease diagnosis to randomization			
<1 year			
>1 year			
Missing			
Number of disease sites per subject			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Presence of target lesions			
No			
Yes			
Missing			
Sum of longest diameter of target lesions			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Prior cetuximab treatment			
No			
Yes			
Missing			

Full dataset contained 347 patients not 361
PROGRAM: I:\LOCAL\UK\Staff Folder\TEJUS DESAI\SAS Training\SAS QC Libraries\BS7006A\BS7006A-Demos v0_1.sas
EXECUTED: October 3, 2016 at 08:29 by td

Table 6.1.2: Demographics for Patients missing from Table 38

	Overall (N=89)	Nivolumab (N=60)	Investigator's Choice (N=29)
Region			
US	[redacted]	[redacted]	[redacted]
European Union	[redacted]	[redacted]	[redacted]
Rest of World	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Age Group			
<65	[redacted]	[redacted]	[redacted]
65<-<75	[redacted]	[redacted]	[redacted]
>75	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Age (continuous)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
Minimum - Maximum	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Race			
White	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Number of lines of prior chemotherapy in the metastatic setting			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
>3	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Baseline ECOG Performance Status			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
PD-L1 Status			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Indeterminate	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
HPV Status			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

```
Full dataset contained 347 patients not 361
PROGRAM: I:\LOCAL\UK\Staff Folder\TEJUS DESAI\SAS Training\SAS QC Libraries\BS7006A\BS7006A-Demos v0_1.sas
EXECUTED: October 3, 2016    at 08:29 by td
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Table 6.1.2 (cont.): Demographics for Patients missing from Table 38

	Overall (N=89)	Nivolumab (N=60)	Investigator's Choice (N=29)
American Joint Committee on Cancer stage at study entry			
III			
IV			
Unknown			
Missing			
Time from initial disease diagnosis to randomization			
<1 year			
>1 year			
Missing			
Number of disease sites per subject			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Presence of target lesions			
No			
Yes			
Missing			
Sum of longest diameter of target lesions			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Prior cetuximab treatment			
No			
Yes			
Missing			

Full dataset contained 347 patients not 361
PROGRAM: I:\LOCAL\UK\Staff Folder\TEJUS DESAI\SAS Training\SAS QC Libraries\BS7006A\BS7006A-Demos v0_1.sas
EXECUTED: October 3, 2016 at 08:29 by td

Table 6.1.3: Demographics for the Patients with data in Table 38 with additional baseline values assumed to be pre-progression

	Overall (N=310)	Nivolumab (N=212)	Investigator's Choice (N=98)
Region			
US			
European Union			
Rest of World			
Missing			
Age Group			
<65			
65<-<75			
>75			
Missing			
Age (continuous)			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Race			
White			
Black			
Asian			
Other			
Missing			
Number of lines of prior chemotherapy in the metastatic setting			
0			
1			
2			
>3			
Missing			
Baseline ECOG Performance Status			
0			
1			
2			
Unknown			
Missing			
PD-L1 Status			
Positive			
Negative			
Indeterminate			
Missing			
HPV Status			
Positive			
Negative			
Unknown			

	Overall (N=310)	Nivolumab (N=212)	Investigator's Choice (N=98)
Missing	[redacted]	[redacted]	[redacted]

Full dataset contained 347 patients not 361
PROGRAM: I:\LOCAL\UK\Staff Folder\TEJUS DESAI\SAS Training\SAS QC Libraries\BS7006A\BS7006A-Demos v0_1.sas
EXECUTED: October 3, 2016 at 08:29 by td

Table 6.1.3 (cont.): Demographics for the Patients with data in Table 38 with additional baseline values assumed to be pre-progression

	Overall (N=310)	Nivolumab (N=212)	Investigator's Choice (N=98)
American Joint Committee on Cancer stage at study entry			
III			
IV			
Unknown			
Missing			
Time from initial disease diagnosis to randomization			
<1 year			
>1 year			
Missing			
Number of disease sites per subject			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Presence of target lesions			
No			
Yes			
Missing			
Sum of longest diameter of target lesions			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Prior cetuximab treatment			
No			
Yes			
Missing			

Full dataset contained 347 patients not 361
PROGRAM: I:\LOCAL\UK\Staff Folder\TEJUS DESAI\SAS Training\SAS QC Libraries\BS7006A\BS7006A-Demos v0_1.sas
EXECUTED: October 3, 2016 at 08:29 by td

Table 6.1.4: Demographics for the Patients missing from Table 38 despite additional baseline values assumed to be pre-progression

	Overall (N=37)	Nivolumab (N=24)	Investigator's Choice (N=13)
Region			
US			
European Union			
Rest of World			
Missing			
Age Group			
<65			
65<-<75			
>75			
Missing			
Age (continuous)			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Race			
White			
Black			
Missing			
Number of lines of prior chemotherapy in the metastatic setting			
0			
1			
2			
Missing			
Baseline ECOG Performance Status			
0			
1			
2			
Missing			
PD-L1 Status			
Positive			
Negative			
Indeterminate			
Missing			
HPV Status			
Positive			
Negative			
Unknown			
Missing			

Full dataset contained 347 patients not 361

PROGRAM: I:\LOCAL\UK\Staff Folder\TEJUS DESAI\SAS Training\SAS QC Libraries\BS7006A\BS7006A-Demos v0_1.sas
EXECUTED: October 3, 2016 at 08:29 by td

Table 6.1.4 (cont.): Demographics for the Patients missing from Table 38 despite additional baseline values assumed to be pre-progression

	Overall (N=37)	Nivolumab (N=24)	Investigator's Choice (N=13)
American Joint Committee on Cancer stage at study entry			
III			
IV			
Missing			
Time from initial disease diagnosis to randomization			
<1 year			
>1 year			
Missing			
Number of disease sites per subject			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Presence of target lesions			
Yes			
Missing			
Sum of longest diameter of target lesions			
N			
Mean (SD)			
Median (Q1, Q3)			
Minimum - Maximum			
Missing			
Prior cetuximab treatment			
No			
Yes			
Missing			

Full dataset contained 347 patients not 361
PROGRAM: I:\LOCAL\UK\Staff Folder\TEJUS DESAI\SAS Training\SAS QC Libraries\BS7006A\BS7006A-Demos v0_1.sas
EXECUTED: October 3, 2016 at 08:29 by td

Summary of Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) with 10% Cutoff
All Treated Subjects - Excluding Cetuximab Subjects

System Organ Class (%) Preferred Term (%)	NIVOLUMAB 3 mg/kg N = 236			INVESTIGATOR CHOICE N = 98		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

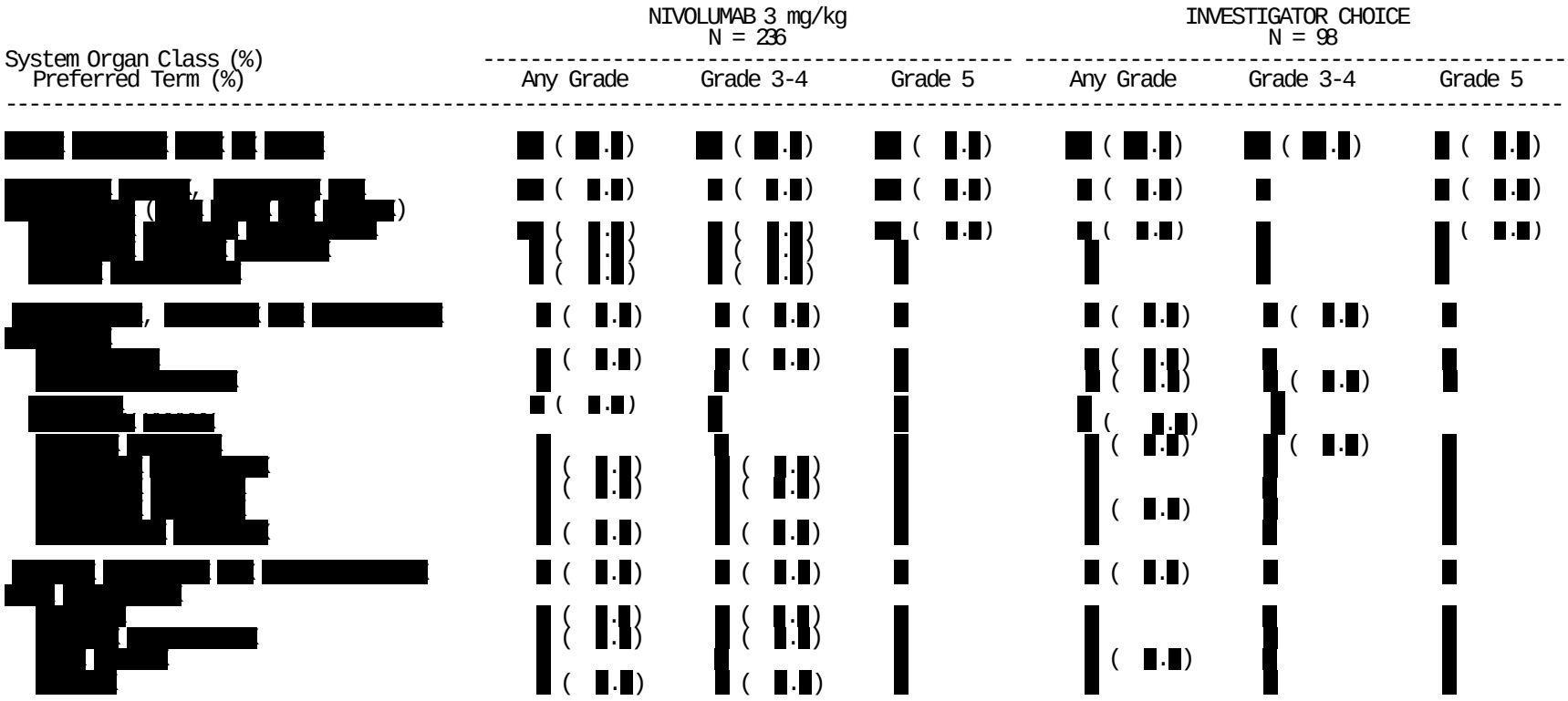
MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program: /gbs/prod/clin/programs/ca/209/141/mma-mauk20160808/rpt/rt-ae-aecatxc-v01.sas 03OCT16:14:01:00

Summary of Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) with 10% Cutoff
All Treated Subjects - Excluding Cetuximab Subjects

System Organ Class (%) Preferred Term (%)	NIVOLUMAB 3 mg/kg N = 236			INVESTIGATOR CHOICE N = 98		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program: /gbs/prod/clin/programs/ca/209/141/mma-mauk20160808/rpt/rt-ae-aecatxc-v01.sas 03OCT16:14:01:00

Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects - Excluding Cetuximab Subjects



System Organ Class (%) Preferred Term (%)	NIVOLUMAB 3 mg/kg N = 236			INVESTIGATOR CHOICE N = 98		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
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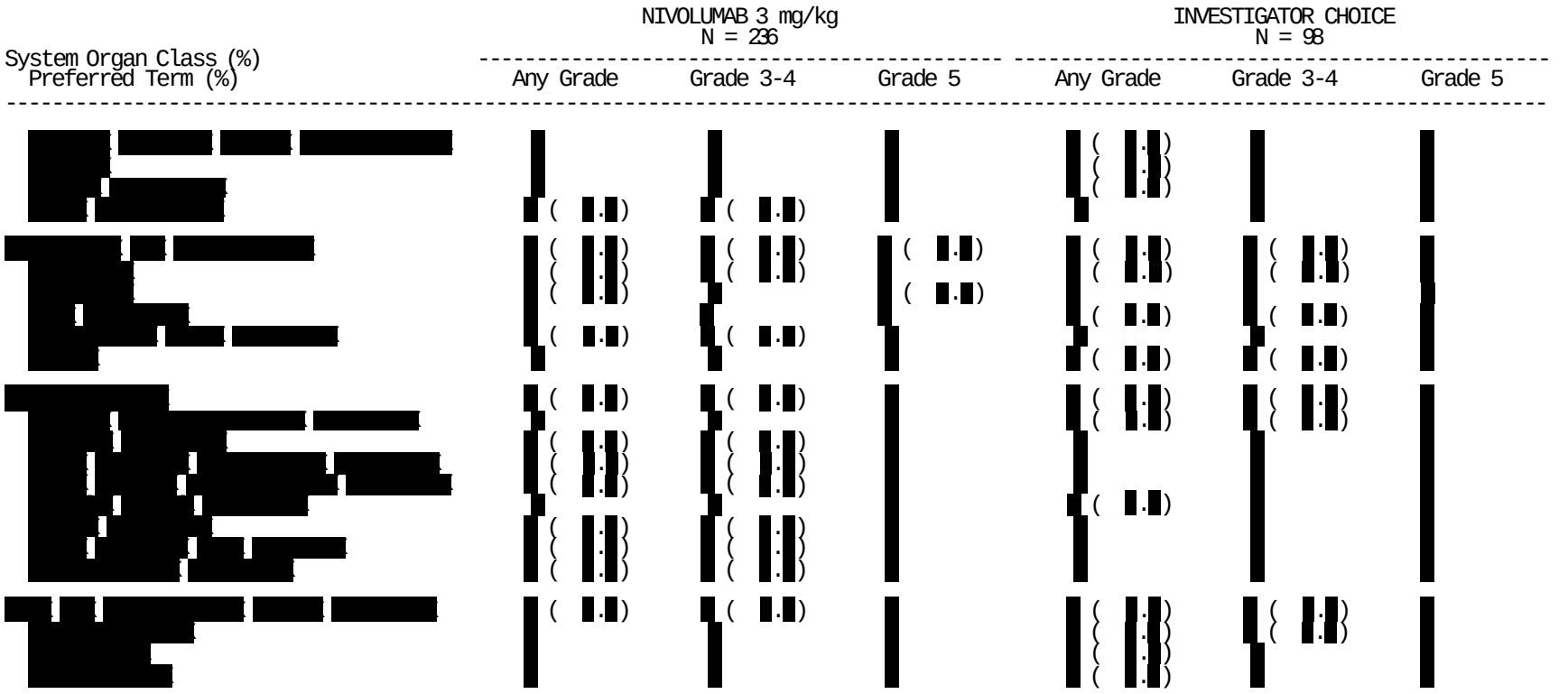
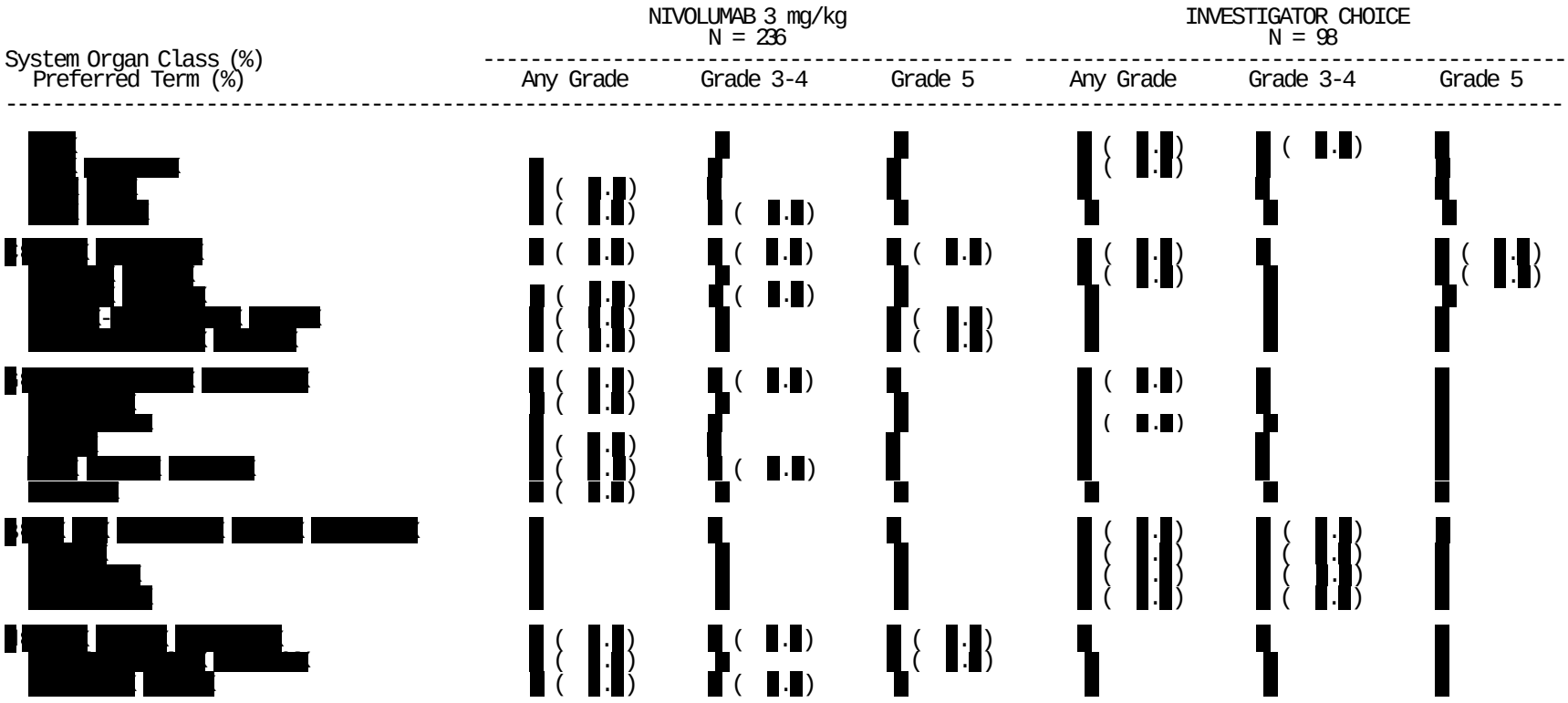
Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects - Excluding Cetuximab Subjects



System Organ Class (%) Preferred Term (%)	NIVOLUMAB 3 mg/kg N = 236			INVESTIGATOR CHOICE N = 98		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]				([redacted])		
				([redacted])		
				([redacted])		
	([redacted])	([redacted])				
[redacted]	([redacted])	([redacted])	([redacted])	([redacted])	([redacted])	
	([redacted])	([redacted])		([redacted])	([redacted])	
	([redacted])		([redacted])			
				([redacted])	([redacted])	
	([redacted])	([redacted])				
				([redacted])	([redacted])	
[redacted]	([redacted])	([redacted])		([redacted])	([redacted])	
				([redacted])		
	([redacted])	([redacted])				
	([redacted])	([redacted])				
	([redacted])	([redacted])				
				([redacted])		
	([redacted])	([redacted])				
	([redacted])	([redacted])				
	([redacted])	([redacted])				
[redacted]	([redacted])	([redacted])		([redacted])	([redacted])	
				([redacted])		
				([redacted])		
				([redacted])		

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program: /gbs/prod/clin/programs/ca/209/141/mma-mauk20160808/rpt/rt-ae-aedccatxc-v01.sas 03OCT16:14:00:57

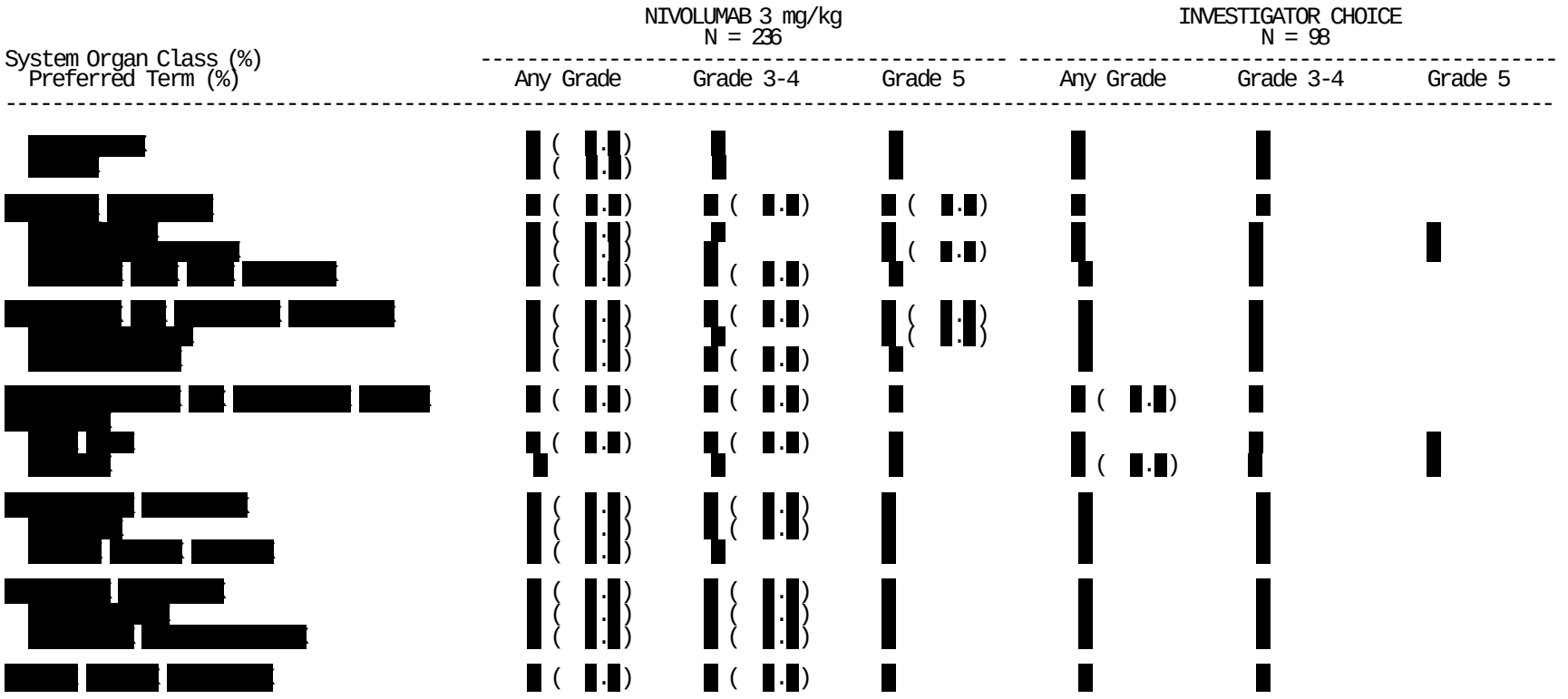
Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects - Excluding Cetuximab Subjects



System Organ Class (%) Preferred Term (%)	NIVOLUMAB 3 mg/kg N = 236			INVESTIGATOR CHOICE N = 98		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program: /gbs/prod/clin/programs/ca/209/141/mma-mauk20160808/rpt/rt-ae-aedccatxc-v01.sas 03OCT16:14:00:57

Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects - Excluding Cetuximab Subjects



System Organ Class (%) Preferred Term (%)	NIVOLUMAB 3 mg/kg N = 236			INVESTIGATOR CHOICE N = 98		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5

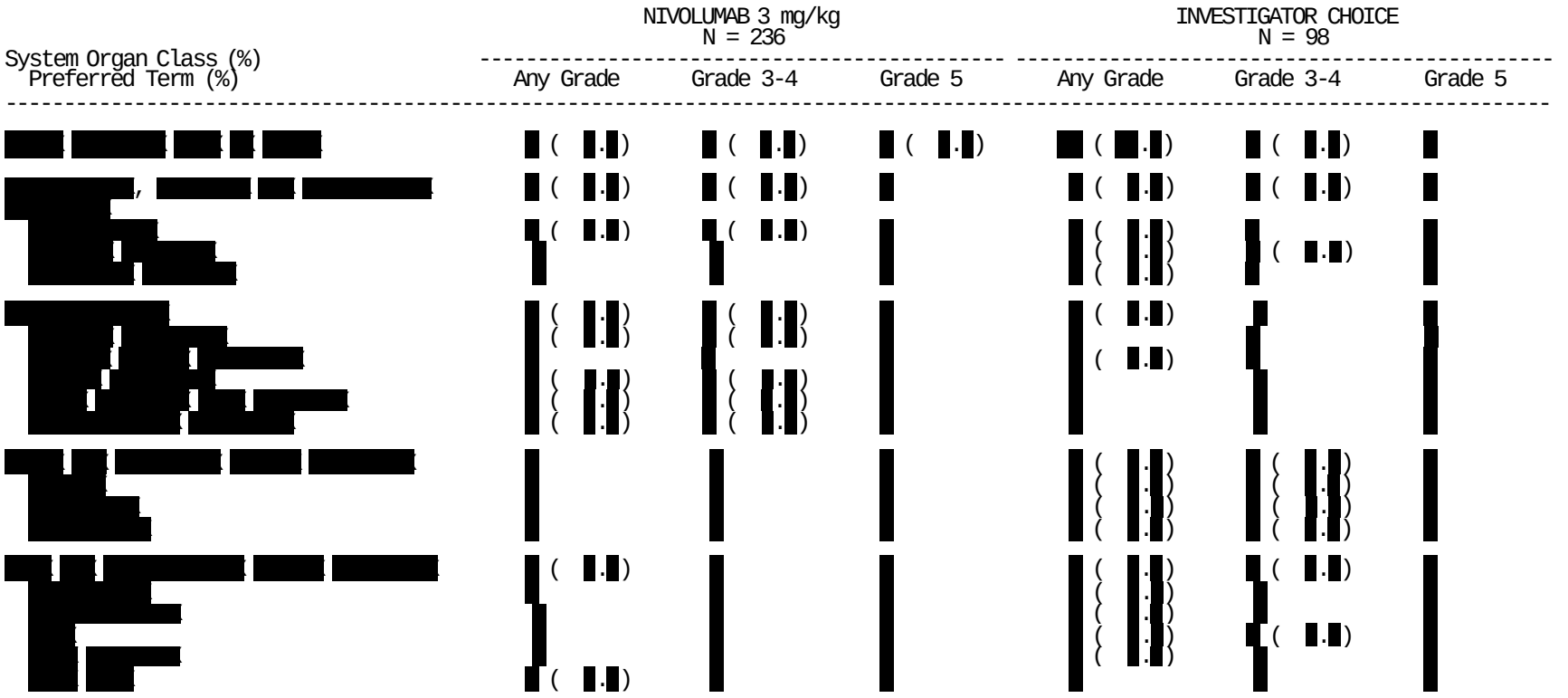
MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program: /gbs/prod/clin/programs/ca/209/141/mma-mauk20160808/rpt/rt-ae-aedccatxc-v01.sas 03OCT16:14:00:57

Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects - Excluding Cetuximab Subjects

System Organ Class (%) Preferred Term (%)	NIVOLUMAB 3 mg/kg N = 236			INVESTIGATOR CHOICE N = 98		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted] ([redacted])	[redacted] ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program: /gbs/prod/clin/programs/ca/209/141/mma-mauk20160808/rpt/rt-ae-aedccatxc-v01.sas 03OCT16:14:00:57

Summary of Drug-Related Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects - Excluding Cetuximab Subjects



System Organ Class (%) Preferred Term (%)	NIVOLUMAB 3 mg/kg N = 236			INVESTIGATOR CHOICE N = 98		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program: /gbs/prod/clin/programs/ca/209/141/mma-mauk20160808/rpt/rt-ae-raedccatxc-v01.sas 03OCT16:14:00:51

Summary of Drug-Related Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects - Excluding Cetuximab Subjects

System Organ Class (%) Preferred Term (%)	NIVOLUMAB 3 mg/kg N = 236			INVESTIGATOR CHOICE N = 98		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]				([redacted])	([redacted])	
				([redacted])	([redacted])	
				([redacted])	([redacted])	
[redacted]	([redacted])	([redacted])				
	([redacted])	([redacted])				
	([redacted])	([redacted])				
[redacted]	([redacted])					
	([redacted])					
[redacted]				([redacted])		
				([redacted])		
[redacted]	([redacted])	([redacted])				
	([redacted])	([redacted])				
[redacted]	([redacted])		([redacted])			
	([redacted])		([redacted])			

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program: /gbs/prod/clin/programs/ca/209/141/mma-mauk20160808/rpt/rt-ae-raedccatxc-v01.sas 03OCT16:14:00:51

Table S.6.12

Protocol: CA209141

Summary of Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects

Select Adverse Events Category: GASTROINTESTINAL ADVERSE EVENT

Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.

Data Sources: ADAE, ADDM
Program Source: S:\RHO\BMS\CA209-141\Clinical\Studies\CA209-141\Biostatistics\Tables\rt-ae-slae-v01.sas 21MAR2016:21:45

Table S.6.12

Protocol: CA209141

Summary of Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects

Select Adverse Events Category: HEPATIC ADVERSE EVENT

Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.

Data Sources: ADAE, ADDM
Program Source: S:\RHO\BMS\CA209-141\Clinical\Studies\CA209-141\Biostatistics\Tables\rt-ae-slae-v01.sas 21MAR2016:21:45

Table S.6.12

Protocol: CA209141

Summary of Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects

Select Adverse Events Category: PULMONARY ADVERSE EVENT

Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.

Data Sources: ADAE, ADDM
Program Source: S:\RHO\BMS\CA209-141\Clinical\Studies\CA209-141\Biostatistics\Tables\rt-ae-slae-v01.sas 21MAR2016:21:45

Table S.6.12

Protocol: CA209141

Summary of Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects

Select Adverse Events Category: RENAL ADVERSE EVENT

Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.

Data Sources: ADAE, ADDM
Program Source: S:\RHO\BMS\CA209-141\Clinical\Studies\CA209-141\Biostatistics\Tables\rt-ae-slae-v01.sas 21MAR2016:21:45

Table S.6.12

Protocol: CA209141

Summary of Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects

Select Adverse Events Category: SKIN ADVERSE EVENT

Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted]			[redacted]	[redacted]	
[redacted]	[redacted]					
[redacted]	[redacted]			[redacted]	[redacted]	
[redacted]	[redacted]			[redacted]	[redacted]	
[redacted]	[redacted]					
[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]			[redacted]	[redacted]	
[redacted]	[redacted]					
[redacted]	[redacted]			[redacted]		

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.

Data Sources: ADAE, ADDM
Program Source: S:\RHO\BMS\CA209-141\Clinical\Studies\CA209-141\Biostatistics\Tables\rt-ae-slae-v01.sas 21MAR2016:21:45

Table S.6.12

Protocol: CA209141

Summary of Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects

Select Adverse Events Category: HYPERSENSITIVITY/INFUSION REACTION

Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.

Data Sources: ADAE, ADDM
Program Source: S:\RHO\BMS\CA209-141\Clinical\Studies\CA209-141\Biostatistics\Tables\rt-ae-slae-v01.sas 21MAR2016:21:45

Table S.6.16

Protocol: CA209141

Summary of Select Endocrine Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All Treated Subjects

Sub Category (%) Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Data Sources: ADAE, ADDM
Program Source: S:\RHO\BMS\CA209-141\Clinical\Studies\CA209-141\Biostatistics\Tables\rt-ae-slaee-v01.sas 21MAR2016:21:48

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy ID971

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: The Swallows Head & Neck Cancer Support Charity

Your position in the organisation: [redacted]

Brief description of the organisation: We support patients, carers and family members dealing with the cancer journey plus look to purchase valuable equipment for local cancer centres dealing with H&N Cancer – currently support in excess of 1500 like-minded people and the most expensive equipment purchased was £31,000 – we self fund

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

You learn to live beyond cancer and understand all the side effects treatment leaves you with.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Patient experience and support in recovery and beyond

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these

treatments and which are preferred and why?

We are all either patients or carers who have been treated by the NHS and the wonderful service available in cancer centres. Radiotherapy, Chemotherapy, Surgery are all first class but after support services are not so good.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

1. Better outcome

2. Quality of life

3. Less side effects during and after treatment

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Not known at this stage

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Please list any concerns patients or carers have about the treatment being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ ~~Yes~~ ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Language and culture impact

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

not sure

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Improve patient outcome
- Improve patient experience

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] submitting on behalf of:

Name of your organisation: NCRI-ACP-RCP-RCR

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

At present, the first-line systemic treatment for recurrent or metastatic squamous-cell carcinoma of the head and neck is platinum-based chemotherapy +/- cetuximab. Once patients have failed platinum-based chemotherapy, there is no standard second line chemotherapy although taxane-based chemotherapy is typically used. There is some variation on the choice of second line chemotherapy, e.g. paclitaxel or docetaxel and either single agent (weekly versus three weekly) and in combination with another platinum-based chemotherapy such as carboplatin. The second line chemo have a poor objective response, typically less than 20% and there are significant toxicities associated with these chemotherapies. Increasingly, patients are participating in clinical trials (esp immunotherapy trials) after failure with platinum-based chemotherapy.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Yes, some of the head and neck cancer patients have a non-SCC histology and that disease behaves differently. In addition, we sometime see patients with unknown primaries. These patients are usually excluded from ongoing clinical trials.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Nivolumab should be used in dedicated cancer centre because of the potential side effects and they need to be monitored by specialist.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

It is currently available for melanoma patients in the UK.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

http://www.uptodate.com/contents/treatment-of-metastatic-and-recurrent-head-and-neck-cancer

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Some of the patients who have failed platinum-based chemotherapy may not want or tolerate further chemotherapy. The recent phase III CheckMate-141 study (presented at the 2016 AACR Annual Meeting trial) has shown that nivolumab improves survival compared to second-line chemotherapy (investigator's choice of cetuximab, methotrexate, or docetaxel). The median OS with nivolumab was 7.5 months compared with 5.1 months with investigator's choice of therapy (HR, 0.70; 95% CI, 0.51-0.96; P = .0101). Additionally, the 1-year OS rates were 36% with nivolumab compared with 16.6% for investigator's choice. The adverse events (AEs) were also significantly less with nivolumab versus investigator's choice, specifically for grade 3/4 events (13.1% vs 35.1%). Therefore, nivolumab may represent a better alternative to second-line chemotherapy and will be more acceptable to majority of the patients compared to chemotherapy. The treatment will be used as a single agent and the patients will be assessed for suitability of the drug according to the inclusion and exclusion criteria of the recent RCT which showed an overall survival benefit.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Once the patients are on the treatment, they will be monitored closely for clinical benefit and side effects in addition to regular scans around every 6-9 weeks to assess for treatment response. The drug will only be continued as long as patients are gaining benefit (ie regressed or stable disease) with acceptable and tolerable side effects.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

http://www.ncbi.nlm.nih.gov/pubmed/27217382

We only have abstract related to findings from the phase III CheckMate-141 study presented at the 2016 AACR Annual Meeting. Based on the information that we have, nivolumab was compared with second-line chemotherapy (investigator's choice of cetuximab, methotrexate, or docetaxel) in patients with head and neck squamous cell carcinoma refractory to platinum-based chemotherapy. Docetaxel would be an acceptable second line treatment. We tend to use methotrexate as third line or not use it at all in the UK. We are not allowed to give cetuximab as second line as it is not funded by CDF, nor by NHS. However, the trial did use docetaxel as second-line which will be our standard of care in the UK. The outcome measure was overall survival which is the most important and objective outcome.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

In the CheckMate-141 study, the adverse events (AEs) were also significantly less with nivolumab versus investigator's choice, specifically for grade 3/4 events (13.1% vs 35.1%). Therefore, nivolumab may not worsen the quality of life more than second-line chemotherapy.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

http://www.ascopost.com/News/41639

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Nivolumab is already routinely given in the NHS for melanoma patients so if this drug is introduced in the NHS, some additional training to head and neck specialists is required but this can be delivered quickly. Some head and neck clinicians have already used the agent in clinical trials. Until NICE recommends its use, the patients will continue to have second-line chemotherapy or best supportive care or participating in a clinical trial.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

The main impact will be on head and neck cancer patients with non-squamous cell carcinoma or unknown primary. These patients were excluded in the study and it is likely that this drug may not recommended for these patients. However, it is not uncommon for these patients to request immunotherapies like nivolumab.

The second impact is that patients with first line treatment will wish to try it, although the results of trials are not yet available. Furthermore, PS-II patients were also excluded from these trials but may benefit from having it.

NHS England submission on the appraisal of nivolumab for patients with head and neck cancer previously treated with platinum-based chemotherapy

1. Patients with squamous cell head and neck cancer can have platinum-based chemotherapy for several differing indications: as adjuvant treatment after surgery when it is combined with concurrent radiotherapy, as primary treatment when combined with concurrent radiotherapy, as neo-adjuvant treatment prior to surgery/radiotherapy/radiotherapy with concurrent chemotherapy or as palliative treatment for recurrent or metastatic disease.
2. Further active treatment of disease that has progressed following platinum-based chemotherapy depends on 3 main factors: 1) the response to previous treatment, 2) the interval between completion of previous platinum-based chemotherapy and subsequent disease progression and 3) the comorbidities of the patient. Patients who have had a good response to previous chemotherapy and who have relapsed after a substantial treatment-free interval will often respond again to platinum-based chemotherapy. Patients who have had a previous poor response to chemotherapy and who are fit and highly motivated for uncertain and very short gains from further chemotherapy can be offered single-agent chemotherapy. There is no standard single agent regimen in this circumstance as no one treatment is clearly superior to another.
3. The key inclusion criteria for the Checkmate-141 study was for patients to have had suffered progressive disease within 6 months of the last dose of platinum-based chemotherapy in any of the categories of treatment outlined above. The prognosis of such patients is poor as is demonstrated by the short median survival duration in the control arm in Checkmate-141 of treatment of physician's choice.
4. The wording of the marketing authorisation could be very important to this appraisal if there is any stipulation as to the need for previous treatment to have included the use of cetuximab for those patients treated with prior palliative platinum- and cetuximab-based combination chemotherapy. The reason for this is that the use of cetuximab does not (yet) carry a NICE recommendation for its incorporation in head and neck cancer chemotherapy.
5. NHS England notes that there appears to be some platueauing evident on the tails of the Kaplan-Meier plots of progression-free survival (PFS), duration of treatment and overall survival (OS). It appears that about 10% of patients have particularly durable responses to treatment but the numbers of patients at risk are very small beyond 15-18 months and thus conclusions as to such a group in the longer term are subject to considerable uncertainty.
6. Nivolumab thus offers small gains to most patients with fewer side-effects than chemotherapy although it is important to state that small numbers of patients treated with nivolumab suffer important and potentially severe immune-mediated

reactions to nivolumab. A very modest proportion of patients gain significantly more benefit but as yet there is no robust was of identifying these electively.

7. NHS England would be able to commission a 2 year treatment stopping rule if NICE includes this as part of any recommendation.
8. NHS England does not regard nivolumab in the treatment of recurrent squamous head and neck cancer as a step change in the treatment of the disease: benefits are short-lived for the majority of patients and the proportion of patients that gains much more impact from nivolumab is small and (so far) cannot be identified prior to the start of treatment.

[redacted]

[redacted] NHS England Chemotherapy Clinical Reference Group and [redacted] for the Cancer Drugs Fund

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: PROFESSOR KEVIN HARRINGTON

Name of your organisation: THE ROYAL MARSDEN HOSPITAL/THE INSTITUTE OF CANCER RESEARCH

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **NO**
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NO

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There is no current gold-standard treatment for patients with recurrent or metastatic (R/M) squamous cell cancer of the head and neck after platinum chemotherapy. Patients tend to be treated with a range of approaches – from best supportive care to single-agent chemotherapy/biotherapy (methotrexate, docetaxel/paclitaxel, cetuximab) – based on local practice and clinician choice. All of the active therapy options are associated with very significant toxicity and relatively low response rates.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with relapsed disease within 6 months of completing definitive chemoradiation or post-operative chemoradiation have a dismally poor prognosis. Patients with HPV+ve R/M disease have a better prognosis, although in the platin-refractory setting, their outcome is also poor. Patients with HPV+ and/or PD-L1+ (>1% expression) tumours have a better prognosis.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This technology should be used in specialist hospital centres, where there is experience of using immuno-oncology agents and expertise in managing their side effects. The range of auto-immune side effects may require addition support from other medical specialists (eg dermatology, endocrinology, gastro-enterology, neurology).

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

This technology is available in other disease types (melanoma, lung) but not for head and neck cancer.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Not relevant.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The treatment will be significantly more easy to use. It is associated with an improvement in overall survival and quality of life. The toxicity profile is favourable relative to standard chemotherapy.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

There is evidence of benefit being greatest in HPV+ and PD-L1+ tumours, although benefit is not restricted to these groups.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The use of the experimental arm (nivolumab) and the investigator's choice chemotherapies in CHECKMATE-141 reflected current practice in the UK. The results are applicable to the UK setting. The most important finding was the improvement in overall survival. QoL outcomes were significantly improved with nivolumab.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The side effect profile of nivolumab is distinct from that seen with standard chemotherapy. The auto-immune effects are relatively uncommon and usually manageable according to well developed algorithms.

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Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I do not see any issues with equality and diversity in regard to the use of nivolumab.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must

include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The peer-reviewed data will be published in the coming months.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

I do not identify any issues in this regard

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Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Anthony Kong

Name of your organisation: University of Birmingham and University Hospital Birmingham NHS Trust

Are you (tick all that apply):

√ a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
None

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Once recurrent or metastatic head and neck cancer patients have progressed on previous platinum based chemotherapy, the prognosis is poor and usually less than 1 year. There is no standard second line or third line therapy for these patients and there is great variation between different centres. For second or third line chemotherapy, single agent taxane (paclitaxel or docetaxel) +/- another platinum chemotherapy or methotrexate has been used in patients who still have relatively good performance status. However, some of these patients may have deteriorating or poor performance status and further combination chemotherapy treatment may be poorly tolerated or not appropriate. For patients who are unfit to have palliative chemotherapy, best supportive case may be the best and kindest option for them since palliative chemotherapy may worsen their quality of life without survival benefit. This decision needs to be made by the doctors and patients together, focusing on the benefits of palliative chemotherapy versus the risks of treatment toxicity.

Selected patients that are not fit for chemotherapy may benefit from immunotherapy, i.e. the technology that is evaluated. Patients treated with immunotherapy can have significant and serious side effects and therefore, this needs to be treated in specialist cancer centre, requiring input from oncologists, surgeons, nurses, pharmacists and other health care professionals (nutritionist, speech therapists) that look after the patients.

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The recent phase III CheckMate-141 study (Ferris R, et al NEJM Oct 2016) has shown that Nivolumab improves overall survival (OS) compared to second-line chemotherapy (investigator's choice of cetuximab, methotrexate, or docetaxel). The median OS with nivolumab was 7.5 months compared with 5.1 months with investigator's choice of therapy (HR, 0.70; 95% CI, 0.51-0.96; P = .0101). Additionally, the 1-year OS rates were 36% with nivolumab compared with 16.6% for investigator's choice. The adverse events (AEs) were also significantly less with nivolumab versus investigator's choice, specifically for grade 3/4 events (13.1% vs 35.1%). In addition, while the physical, role, and social functioning of the patients treated with Nivolumab was stable, it was meaningfully worse in the standard-therapy group receiving investigator's choice of cetuximab, methotrexate or docetaxel.

Therefore, nivolumab may represent a better alternative to second-line chemotherapy and will be more acceptable to majority of the patients compared to chemotherapy.

The most important outcome is that nivolumab improves overall survival a gold standard outcome measure and has less side effects compared to chemotherapy or cetuximab.

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Single Technology Appraisal (STA)

In regards to CheckMate-141 study, one thing to note is that while we use docetaxel as second line treatment in the UK, most oncologists don't use methotrexate or only occasionally use it as third line. We don't use cetuximab monotherapy as second or third line treatment.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; **No**
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; **No**
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities **No**

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts
CheckMate-141 study did not exclude particular group of people protected by legislation.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Ferris R, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. NEJM 9 Oct 2016:
http://www.nejm.org/doi/full/10.1056/NEJMoa1602252#t=article

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

I anticipated that if this technology were to be recommended, the treatment will be used as a single agent and the patients will be assessed for suitability of the drug according to the inclusion and exclusion criteria of the recent CheckMate-141 study (Ferris R, et al NEJM Oct 2016):

Inclusion criteria:
Eligible patients had histologically confirmed, recurrent squamous-cell carcinoma of the head and neck (including metastatic disease) of the oral cavity, pharynx, or larynx that was not amenable to curative treatment; tumour progression or recurrence within 6 months after the last dose of platinum-containing chemotherapy administered as adjuvant therapy or in the context of primary or recurrent disease; an age of at least 18 years; an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale from 0 to 5, with higher numbers indicating greater disability); adequate bone marrow, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.14

Major exclusion criteria
active brain metastases, autoimmune disease, or systemic immunosuppression; known human immunodeficiency virus or hepatitis B or C virus infection; and previous therapy targeting T-cell costimulating or immune-checkpoint pathways.

Therefore, some patients may be excluded if their disease is clearly different from the patient group included in CheckMate-141 study.

In terms of delivery, NHS is now used to deliver this drug or similar drug as it is already routinely given to other cancer patients (e.g. lung cancer and melanoma patients). There have been several educational meetings and training sessions on the management of toxicities related to this drug or similar drug for staff in the NHS.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy

Produced by Kleijnen Systematic Reviews Ltd. (KSR) in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)

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Declared competing interests of the authors
None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Nigel Armstrong acted as project lead as well as systematic reviewer and health economist on this assessment, critiqued the clinical effectiveness methods and evidence as well as the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Xavier Pouwels, Remziye Zaim and Ching-Yun Wei acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Robert Wolff and Rob Riemsma acted as systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore and Maiwenn Al acted as health economists on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

5-FU	5-Fluoruracil
AE	Adverse Events
AHNS	American Health and Neck Society
AIC	Akaike information criterion
AMCP	Academy of Managed Care Pharmacy
ASCO	American Society of Clinical Oncology
ASCO-QoC	ASCO Quality Care Symposium
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	Best overall response
BAHNO	British Association of Head and Neck Oncologists
BSA	Body surface area
BUP	Buparlisib
CADTH	Canadian Agency for Drugs and Technologies in Health
CCT	Controlled clinical trial
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CMR	Cochrane Methodology Register
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DALY	Disability-adjusted life year
DMC	Data monitoring committee
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EHNS	European Society of Medical Oncologists
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group performance status
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EORTC H&N35	European Organisation for Research and Treatment of Cancer head and neck questionnaire
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
EUR	Erasmus University Rotterdam
FDA	US Food and Drug Administration
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health Related Quality of Life

HTA	Health Technology Assessment
i.v.	Intravenous
IC	Investigator's choice
ICER	Incremental cost effectiveness ratio
ICUR	Incremental cost utility ratio
IDMC	Independent data monitoring committee
IPCW	Inverse probability of censoring weights
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to Treat
IVRS	Interactive voice response system
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LOE	Languages other than English
LY	Life year
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
mg	Milligram
MI	Multiple imputation
MRI	Magnetic resonance imaging
N/A	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
NSCLC	Non-small cell lung cancer
OCIU	Oxford Cancer Intelligence Unit
ORR	Objective response rate
OS	Overall survival
PAC	Paclitaxel
PAS	Patient access scheme
PBO	Placebo
PD	Progressed disease
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PF	Progression-free
PFS	Progression-free survival
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PS	Performance status
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
Q2W	Once every two weeks
Q3W	Once every three weeks
QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of life
QW	Once weekly
R/M	Relapsed or metastatic
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SC	Subcutaneous
SCC	Squamous cell carcinoma
SCCHN	Squamous cell carcinoma of the head and neck
SD	Standard deviation

SE	Standard error
SEER	Surveillance, Epidemiology, and End Results Program
SF-36	Short form 36
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
STA	Single Technology Appraisal
UMC	University Medical Centre
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
TTD	Time to treatment discontinuation
TTF	Time to failure
TTO	Time trade off
TTP	Time to progression
TTR	Time to response
UK	United Kingdom
USA	United States of America
VEGF	Vascular endothelial growth factor

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

According to the company submission (CS), the anticipated indication for nivolumab as a treatment for squamous cell carcinoma of the head and neck (SCCHN) is: *"Nivolumab (Opdivo®) is indicated for the treatment of recurrent or metastatic squamous-cell cancer of the head and neck after platinum-based therapy in adults".* This is precisely the population in the scope issued by the National Institute for Health and Care Excellence (NICE).

However, there seems to be a mismatch between this and the main trial, CheckMate 141. According to the response to the clarification letter, the Evidence Review Group (ERG) understands that the company believes that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy, which is consistent with the inclusion criteria for the trial.

The comparators listed in the decision problem are in accordance with the scope and they are those that are compared in the cost effectiveness analysis (CEA). The intervention and outcomes are also in line with the scope.

However, there were several deviations from the scope in the clinical effectiveness section. Firstly, the company provided no evidence as to the effectiveness of paclitaxel. Secondly, the main trial randomised patients either to nivolumab or to an 'investigator choice' (IC) arm, which allowed clinicians to decide which of three treatments to prescribe thus preventing an intention to treat (ITT) analysis of nivolumab versus any of the comparators individually. Thirdly, IC in the main trial also included cetuximab, which is not within scope. The effects of these deviations are summarised in Section 1.2.

According to the CS, *"an application for a marketing authorisation in Europe for the indication detailed in this submission was submitted to the EMA on* [redacted] *and a positive opinion from the CHMP is anticipated on* [redacted] *".*

1.2 Summary of clinical effectiveness evidence submitted by the company

The evidence base for the clinical efficacy of nivolumab in the treatment of SCCHN consists of one randomised controlled trial (RCT), CheckMate 141. The company report that only this RCT was included in the systematic review as it was the only one that reported the efficacy of nivolumab.

CheckMate 141 was a phase III multicentre randomised, open-label, active-controlled, parallel group trial comparing the efficacy and safety of nivolumab with IC, which included choice at the clinician's discretion of docetaxel, methotrexate or cetuximab. The primary endpoint for the CheckMate 141 trial was overall survival (OS), which demonstrated a significant improvement in the nivolumab arm compared to the IC arm (hazard ratio (HR), 0.70 [97.73% confidence interval (CI) 0.51 to 0.96]; stratified (by prior cetuximab use) log-rank test p-value=0.0101). There was no statistically significant difference in progression free survival (PFS; HR 0.89, 95% CI 0.7 to 1.1). Table 1 shows a summary of effectiveness of nivolumab versus IC, as well as the individual treatments.

The CS and clinical study report (CSR) also report three quality of life (QoL) instruments: the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC General Cancer Module (QLQ-C30)), the EORTC Head and Neck Specific Module (QLQ-H&N35) and the European Quality of Life questionnaire (EQ-5D). Results were presented for various follow-up times, but the company defined two time points: Follow-up 1 as last dose date to last dose date +58 days and Follow-up 2 as last dose date +59 days to last dose date +102 days. Generally, differences between groups were minimal at first follow-up (Table 2). There were bigger differences at second follow-up, but numbers of patient included at second follow-up were very small (EORTC-QLQ-C30 Global health status: n=5 and n=2 for nivolumab and IC respectively; EORTC QLQ-H&N35 – Pain: n=6 and n=2 for

nivolumab and IC respectively). The utility values obtained from the EQ-5D-3L were presented as part of the economic analysis of nivolumab versus comparators and presented in the main body of the report.

Nivolumab was generally well tolerated by patients in CheckMate 141 compared to IC of therapy, with a lower proportion of patients receiving nivolumab experiencing Grade 3-4 all-causality adverse events (AEs), serious adverse events (SAEs) and discontinuation due to AEs (Table 3).

Table 1: Overview of clinical effectiveness results from CheckMate 141 – all-randomised population

Outcome[a]	Nivolumab (n=240)	IC (n=121)	Methotrexate (n=52)	Docetaxel (n=54)	Cetuximab (n=15)
Overall Survival					
Deaths, n (%)	133 (55.4)	85 (70.2)	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)	[redacted]	[redacted]	[redacted]
HR for death with nivolumab (97.73% CI; p-value)[b]	0.70 (0.51, 0.96; p=0.0101)		0.64 (0.43, 0.96)[c] [redacted]	0.82 (0.53, 1.28)[c] [redacted]	0.47 (0.22, 1.101)[c] [redacted]
1-year survival rate, % (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)	NR	NR	NR
Progression-free survival[e]					
Events, n (%)	190 (79.2)	103 (85.1)	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	2.0 (1.9, 2.1)	2.3 (1.9, 3.1)	[redacted]	[redacted]	[redacted]
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)		[redacted]	[redacted]	[redacted]
6-month PFS rate, % (95% CI)	19.7 (14.6, 25.4)	9.9 (5.0, 16.9)	NR	NR	NR

Source: Gillison 2016[27], Ferris 2016[26] and CheckMate 141 CSR (7th June 2016)[25]

Notes: [a] Results are presented from the initial database lock of 18th December 2015 for OS and from the database lock of 5th May 2016 for PFS and tumour response; [b] The pre-specified boundary for statistical significance required the p-value to be less than 0.0227, 95% CI were 0.53, 0.92; [c] Reported in CS (intended IC): Figure 17, page 71; [d] Reported in CSR (actual treatment): Figure 7.2-2, page 82. [e] Disease progression and tumour response were assessed by the investigator using RECIST version 1.1; [f] Reported in CSR (intended IC): Figure 7.3.1-1, page 89

CI = confidence intervals; CS = company submission; CSR = clinical study report; HR = hazard ratio; IVRS = interactive voice response system; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours; TTR = time to response

Table 2: Quality of life in CheckMate 141

	Nivolumab 3mg/kg (N=240)		Investigator's Choice (N=121)	
	N	**Mean (SD)**	**N**	**Mean (SD)**
EORTC QLQ-C30 – Global health status[a]				
Baseline	188	55.0 (23.64)	91	57.4 (21.21)
FOLLOW-UP 1* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP 2* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-H&N35 – Pain[b]				
Baseline	193	27.8 (27.84)	91	26.2 (27.43)
FOLLOW-UP 1* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP 2* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D – VAS[c]				
Baseline	185	51.2 (27.34)	87	57.9 (29.42)
FOLLOW-UP 1* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP 2* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]

Source: CheckMate 141 CSR (7th June 2016) [a] Table S.10.7; [b] Table S.10.9; [c] S.10.10

Notes: * All questionnaires completed at baseline and on-study have been assigned a time-point. In case a patient has two on-study assessments within the same window, the assessment closest to the time-point was used. And in the case of two assessments at a similar distance to the time-point, the latest one was chosen. In the event where the patient had no assessment at all in a specific window, the observation was treated as missing for that time-point. Follow-up 1 = Last dose date -to Last dose date + 58 days; Follow-up 2 = Last dose date + 59 days to Last dose date +102 days

	Nivolumab 3mg/kg (N=240)		Investigator's Choice (N=121)	
	N	**Mean (SD)**	**N**	**Mean (SD)**
CSR = clinical study report; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire; EORTC QLQ-H&N35 = European Organisation for Research and Treatment of Cancer head and neck questionnaire; EQ-5D = European Quality of Life-5 Dimensions; VAS = visual analogue scale				

Table 3: Summary of safety analysis in CheckMate 141

Adverse event, n (%)[a, b]	Nivolumab (n=236)		IC (n=111)	
Deaths	[redacted]		[redacted]	
Deaths due to study drug toxicity	2 (0.8)[c]		0[d]	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All causality AEs	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related AEs	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
All-causality SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related SAEs	[redacted]	[redacted]	[redacted]	[redacted]
All-causality AEs leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related AEs leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 18 of the CS[1]

Notes: [a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy; [b] AEs were coded using the MedDRA version 18.1. and were graded for severity according to the NCI CTCAE version 4.0; [c] Two deaths in the nivolumab arm (Grade 3 pneumonitis and Grade 5 hypocalcaemia) were assessed as related to study drug; [d] In the IC arm, there was 1 death in a patient with a Grade 5 drug-related AE (lung infection) that was not attributed to study drug toxicity; Database lock of 18th December 2015.

AEs = adverse events; CS = company submission; IC = investigator's choice; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAEs = serious adverse events.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and searches of conference proceedings were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal. The CS and response to clarification provided sufficient details for the ERG to appraise the majority of searches conducted.

The company did seem to include all relevant controlled trials given that the inclusion criteria were broad enough not to exclude on the basis of design or any of the comparators. However, it appears that there is only one RCT that at least approximately matches the population in the scope i.e. CheckMate 141. Unfortunately, it lacks any comparison with one of the comparators defined in the NICE scope, i.e. paclitaxel. Also, it does have some significant limitations, including a comparison not with the comparators in the scope, but with IC, which permits clinician choice of treatment. This therefore means that the ITT analysis prevents an unbiased estimate of the effectiveness of nivolumab versus any of the comparators. It did, however, show a statistically significant advantage in OS versus IC, which might be considered an unbiased estimate versus standard care, but only if IC was made on the same basis as that in clinical practice. However, there is no way of knowing that and it would have to mean that precisely the same proportion of patients was eligible for each of the therapies (methotrexate, docetaxel and cetuximab) as in the trial. To compound the problem, one of the choices was cetuximab, which is not in the scope. Therefore, the ERG considers that the representativeness of the CheckMate 141 trial to clinical practice in the United Kingdom (UK) is highly questionable most particularly in terms of patient characteristics that would determine both intended treatment and prognosis.

The ERG did ask in the clarification letter for analyses to attempt to overcome these two main limitations, i.e. the inclusion of cetuximab and the missing comparison with paclitaxel. In response, the company did demonstrate little effect of the removal of the cetuximab patients, which was likely given the small number (n=15). They also provided three tables, which summarised the design, baseline characteristics and outcomes of five paclitaxel trials. The ERG concluded that, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab. Also, the response to a clarification question regarding the difference in the HRs for OS between the European Union and North America highlighted the difference in percentage receiving each of the treatments in the scope (docetaxel and methotrexate). The ERG would therefore conclude that, whilst it is reasonable to believe that nivolumab extends life expectancy, it is impossible to be confident by how much in comparison to any treatment in the scope or which is considered to be standard care in the UK.

The ERG also identified two issues which might limit the generalisability of results of the CheckMate 141 trial.

1. Based on information in the CS and the response for request for clarification, the prevalence of males in the index population is approximately 70%. It should be noted that 83.1% of the trial population is male. Given that discrepant results are reported for OS (nivolumab versus IC; [redacted], respectively), this issue might influence the applicability of study results to the overall UK population.
2. The ERG noticed differences in the OS HRs between participants from North America and the European Union (EU), i.e. [redacted] and [redacted], respectively. In response to request for clarification, the company offered several explanations, including the lower proportion of human papillomavirus (HPV)-positive and never smoker patients in Europe, an imbalance of HPV status across treatment arms within the European subgroup and differences in choice of IC of therapy. Differences in the recorded baseline characteristics between the EU and North America as well as in the treatments chosen highlights the potential for lack of applicability to the UK.

The ERG considered the company's claim to fulfil the end of life (EOL) criteria and concluded that the first criterion (life expectancy of less than 24 months) has probably been met. It is, however, less clear that the second criterion (extension of life of at least three months) has been met given an advantage of less than three months in terms of median survival, as detailed in the main body of the report.

1.4 Summary of cost effectiveness submitted evidence by the company

The company conducted systematic reviews to identify relevant cost effectiveness studies, health-related quality of life studies, resources and costs studies. The company did not identify any study investigating the cost effectiveness of nivolumab in the population of interest for the current decision problem, and hence developed a *de novo* model.

The company developed a cohort-based partitioned survival model consisting of three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. According to the company, the model structure represents the clinical pathway of care of R/M SCCHN treatment and is consistent with previous economic evaluations submitted to NICE in R/M SCCHN (technology appraisal 172, 2009) and other evaluations of nivolumab appraised by NICE (ID811, ID900). Costs and health-related utilities associated with each health state were calculated per cycle. Costs and disutilities

associated with AEs were estimated per episode and applied only once, at the beginning of the first cycle, based on the proportion of patients in each treatment arm experiencing each AE. A four week cycle length was used over a time horizon of 20 years, which is effectively a life time perspective.

The economic evaluation considers patients with R/M SCCHN who have progressed after platinum-based therapy. The company states this is consistent with the study population of CheckMate 141, and the anticipated indication for nivolumab in SCCHN and the population outlined in the final scope issued by NICE for this appraisal.

Nivolumab was modelled with a posology of 3 mg/kg as a 60 minute infusion (as per the anticipated licensed indication in SCCHN). The licence also specifies that nivolumab treatment should be continued until clinical benefit is no longer observed. This aspect of anticipated use of nivolumab is reflected through the use of the time to treatment discontinuation curve to model time on treatment instead of the PF curve, as nivolumab treatment might be continued after progression based on the RECIST criteria. The comparators in the cost effectiveness model are docetaxel, paclitaxel and methotrexate. It should be noted that docetaxel is assumed to be administered once weekly at a dose of 30 mg/m^2 while in the UK docetaxel is most often administered at a dose of 75 mg/m^2 every three weeks, according to the company. These comparators were modelled using the IC arm of the CheckMate 141 trial, assuming equivalence in terms of treatment effectiveness between docetaxel and methotrexate as well as between docetaxel and paclitaxel.

Parametric time-to-event models were used to estimate OS, PFS and time to treatment discontinuation (TTD). These time-to-event models were estimated in accordance with NICE Decision Support Unit (DSU) guidance. Since the assumption of proportional hazard was not fulfilled, the company decided to fit separate survival curves to each arm of the trial but the same distribution was used in both arms for each outcome.

The impact of AEs on costs and utility was incorporated in the first cycle of the model (once only). Any all-cause Grade 3 or 4 AE was included if the incidence was ≥5% in either arm of the CheckMate 141 trial. Additionally, based on clinical expert feedback, dysphagia, nausea and vomiting, and anorexia were incorporated as well.

Treatment-dependent health state utilities for the progression-free and progressed disease states were derived from the EQ-5D-3L data collected from patients in the CheckMate 141 trial. Patients included in the analysis consisted of the randomised population (n=361) that had any non-missing EQ-5D-3L and tumour response data. This information was available for a total of [redacted] patients in the nivolumab group and [redacted] patients in the IC group. Accounting for those patients who contributed multiple observations, a total of [redacted] and [redacted] observations were obtained in the nivolumab group and IC group, respectively. Note that whilst some patients had multiple measurements, the EQ-5D-3L measurements were assumed to be independent (i.e. neglecting within-subject correlation). Data for both EQ-5D-3L and tumour response in [redacted] were completely missing (i.e. unable to calculate a utility score at any time point/stratified for tumour response). Utility values for PF patients were [redacted] for the nivolumab and IC group, respectively; for PD these utility values were [redacted]. In addition, the impact of AEs on utility was calculated using disutilities for AEs retrieved from the literature.

Resource use and costs included in the company's economic model were based on data from the CheckMate 141 trial, previous technology appraisals and published sources identified in the systematic literature review. Drug acquisition costs were obtained from the British National Formulary for nivolumab and from the electronic market information tool for IC drugs while the costs of drug administration and monitoring for these drugs were based on the National Health Service (NHS)

reference cost schedule. Moreover, the proportion of patients who received subsequent systemic therapy post-discontinuation was based on the CheckMate 141 trial (nivolumab [redacted] and IC [redacted]) whereas the type of subsequent therapy was dependent on initial treatment (docetaxel and/or methotrexate). Health state costs (i.e. disease management costs) in terms of the type of resource and the proportion of patients who received each resource item were based on a UK study identified in the economic systematic literature search. This was similar for the one-off costs for patients that progressed or died. Moreover, the costs of treating AEs were based on NHS reference costs and assumptions used in previous appraisals.

In the company's base-case analysis, nivolumab was more effective than docetaxel, methotrexate and paclitaxel in terms of both quality-adjusted life years (QALYs) and life years (LYs). It should be noted that the QALYs and LYs for docetaxel, methotrexate and paclitaxel were equal (due to the assumption of equivalence) and were estimated based on the IC arm of the CheckMate 141 trial. The main source of QALY and LY benefit from treatment with nivolumab came from an extension in the period of time spent in the PD state. This substantial QALY gain in the PD state with nivolumab is reflective of the improved OS for nivolumab versus IC (with relatively similar PFS), and also the higher utility associated with nivolumab in the PD state.

Nivolumab was also associated with higher life time costs than docetaxel, methotrexate and paclitaxel irrespective of whether the patient access scheme (PAS) for nivolumab was applied. It should be noted that the costs for docetaxel, methotrexate and paclitaxel only differed with regards to the costs of drug acquisition and subsequent therapy. The overall differences in costs between nivolumab with PAS and the comparators were largely (87%) due to higher drug acquisition costs for nivolumab. In the company's base-case analysis (probabilistic), the increased QALYs and costs for nivolumab resulted in ICERs of £35,157, £35,025, and £35,091 versus docetaxel, paclitaxel and methotrexate, respectively.

The cost effectiveness results were generally robust under most of the scenarios and one-way sensitivity analyses conducted by the company. However, in two scenario analyses considering either alternative distributions for OS or alternative distributions for TTD, the incremental cost effectiveness ratios (ICERs) of nivolumab (with PAS) versus the comparators increased to £62,156 - £62,399 and £77,111 - £77,232 respectively. Also, when decreasing the nivolumab utility value for progressed disease in a sensitivity analysis, the ICER increased with almost £18,000. However, it should be noted that, in the original CS, the parameters of the distributions estimating OS, PFS and TTD were not considered in the sensitivity analyses and that the one-way sensitivity analyses were often based on arbitrary estimates of the variance even if empirical estimates were available (e.g. upper and lower quartiles for the NHS reference costs).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The majority of the cost effectiveness searches in the CS were well documented and easily reproducible, and were carried out in line with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. The ERG expressed concerns on the lack of relevant MeSH indexing terms on Embase.com, the restriction to English language only, and the omission of specific searches for the identification of measurement and valuation of health effects data.

The model structure is similar to other oncology assessments as well as similar to previous nivolumab appraisals and seems appropriate for the current decision problem. All AEs were incorporated only once in the first cycle. Although this simplification might underestimate the long-term influence of AEs on the cost effectiveness outcomes, it is expected to have a minor impact on the cost effectiveness results given the relatively small differences between treatments in rates of AEs. Additionally, the population

represented in the cost effectiveness model seems to correspond to the expected licensed indication and the final scope issued by NICE for the current decision problem.

The equivalence assumption between docetaxel and methotrexate as well as between docetaxel and paclitaxel was questioned by the ERG. However, a scenario analysis, provided by the company (clarification letter Table 22), using treatment specific effectiveness estimates for docetaxel and methotrexate (instead of using IC effectiveness), showed that the assumption of equivalence between docetaxel and methotrexate is not likely to be influential in terms of incremental QALYs, incremental costs and the ICER.

The ERG considered the statistical methods used by the company for selecting the distributions for the time-to event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis. However, the ERG has some concerns with the interpretation and validation of the selected time-to-event models. Next to the questionable assumptions of equivalence (discussed above and below in Section 1.7), the selection of the log-logistic distribution for TTD by the company was questioned by the ERG. The ERG used the generalised-gamma distribution in its base-case for two reasons. Firstly, the PFS and TTD curves cross for the IC arm suggesting that there is post-progression treatment which seems implausible for the IC arm, using the generalised-gamma distribution would resolve this issue. Secondly, although there is no clear best option based on the goodness-of-fit statistics, based on visual inspection the ERG would prefer the generalised-gamma as the tail seems more plausible.

Health state utility data for [redacted] of 361 patients ([redacted]) were missing in the company base-case. In response to the clarification question B7, the company identified [redacted] patients who had a baseline EQ-5D score but were not assigned to a health state at baseline and hence not included in the company base-case. The company repeated the calculation of utility values by therapy and by health including these [redacted] patients, under the assumption that these patients were in the pre-progression health state at the time of the baseline measurement (consistent with the inclusion criteria). These health state utility values are used in the ERG base-case. Moreover, it is unclear to the ERG whether the differences in utility between the treatments are due to the differences between the treatments or the selection of cases (i.e. missing cases). Therefore, the ERG base-case used treatment independent utility values.

Regarding resource use and costs, it was unclear to the ERG why the proportions of subsequent treatment were assumed to be treatment independent (also considering the small differences) and an average of the proportions of subsequent therapies from the CheckMate 141 trial was used in ERG base-case. Moreover, the dosing schedule of nivolumab has recently been modified by the US Food and Drug Administration (FDA) from the 3 mg/kg every two weeks to a 240 mg fixed dose every two weeks for the treatment of renal cell carcinoma, metastatic melanoma and non-small cell lung cancer. The influence of this modified dosing scheme on the cost effectiveness results was explored by the ERG in an exploratory analysis. Additionally, the administration schedule of docetaxel applied in the model is not representative of UK daily practice. Therefore, the ERG used the once every three week administration schedule of docetaxel (75 mg/m^2 per administration) instead of the once weekly administration schedule (30 mg/m^2 per administration) in its base-case analysis because this schedule is more routinely used in the UK and because there is no evidence to support a difference in efficacy between the two docetaxel schemes.

Given that PFS was similar between nivolumab and IC while nivolumab resulted in a clinically relevant median OS benefit, a post-progression benefit of nivolumab is to be expected. However, it is noteworthy that in the company's base-case, 83% of the estimated QALY gain (87% of the estimated LY gain) is attributable to the period after disease progression has been confirmed. Moreover, 78% of the estimated LY gain is attributable to the period after treatment discontinuation. This implies that additional benefit

continues to accrue to patients whose disease has progressed and/or to patients that no longer receive nivolumab. In response to the clarification letter, the company provided cost effectiveness acceptability curves that considered all treatments simultaneously and showed that with the PAS, the probability that nivolumab is cost effective is [redacted] and [redacted] at thresholds of £30,000 and £50,000 per QALY respectively.

The company mentioned that external and cross validation were not possible. The ERG believes that the lack of external validation of long-term outcomes hampers the interpretation of the CS, particularly given the lack of evidence to support the long-term post-progression benefits of nivolumab.

In conclusion, given the ERG base-case ICERs are estimated to be around £50,000 per QALY gained, the large uncertainty regarding extrapolation and post-progression benefits in combination with the lack of external validation of long-term outcomes and the doubt about the generalisability of the CheckMate 141 trial results to the UK the decision, uncertainty around the cost effectiveness of nivolumab remains substantial.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal. The CS and response to clarification provided sufficient details for the ERG to appraise the searches. Efforts were made to identify e-Pub ahead of print publications in PubMed for the clinical and cost effectiveness searches. Additional searches of conference proceedings were conducted.

Using broad inclusion criteria, the company identified a single RCT (CheckMate 141, n=361) which reported results for all outcomes defined in the scope defined by NICE.

The economic model structure is similar to other oncology assessments as well as similar to previous nivolumab appraisals and seems appropriate for the current decision problem. Moreover, the ERG considered the statistical methods used by the company for selecting the distributions for the time-to event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis.

1.6.2 Weaknesses and areas of uncertainty

The ERG was concerned about the language bias of restricting searches to English language only as this is not in line with current best practice. Significant differences were noted between the original and update searches for clinical effectiveness studies. As the ERG was unable to access Embase.com, it was not possible to determine whether this impaired the performance of the CS searches. There were limitations with the use of indexing terms on Embase.com searches, as strategies only used EMTREE. Although some mapping between indexing terms does take place on Embase.com it is possible that relevant MEDLINE indexing terms (MeSH) will not be included in the search, and potentially relevant records could be missed. Searches for adverse events were based on the clinical effectiveness search strategies which included study design filters. It is possible that relevant evidence may have been missed as a consequence of this. Of concern for the cost effectiveness review, no resource use or cost searches were conducted, and data were therefore not systematically retrieved.

As outlined before, the ERG considers that the representativeness of the CheckMate 141 trial to UK clinical practice is highly questionable most particularly in terms of patient characteristics that would determine both intended treatment and prognosis. Given that, it is impossible to be confident to estimate efficacy and safety compared to any treatment in the scope or standard care in the UK.

It should be noted that the quality assessment of CheckMate 141 identified a few issues which might influence the validity of the findings, i.e. the lack of blinding as well as imbalances in the drop-outs between treatment and comparator.

In addition, it was unclear how many reviewers were involved in the systematic review to identify clinical effectiveness evidence. The lack of a second reviewer in systematic reviews can increase the risk of bias and error in the review.

In the economic model, the reliance on an equal effectiveness assumption for all comparators (i.e. docetaxel, methotrexate and paclitaxel) was considered as one of the main weaknesses. Moreover, the approach to modelling AEs was not reflective of best practices.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate respectively. The most influential adjustments/corrections made by the ERG were 1) using a generalised-gamma distribution for estimating TTD; 2) using treatment independent utilities for PFS and PD health state utility values and; 3) using a dose and frequency of administration for docetaxel (75 mg/m^2 once every three weeks) consistent with UK clinical practice. Moreover, in an exploratory analysis, the ERG used an adjusted dosage for nivolumab (fixed dose of 240 mg every two weeks) that was recently recommended by the FDA for renal-cell carcinoma, metastatic melanoma, and non-small cell lung cancer. This exploratory analysis, which was performed conditional upon the ERG base-case, resulted in ICERs (with PAS) of £50,160 to £53,439. Moreover, applying shorter time horizons, to explore the impact of the extrapolating estimated benefits of costs, resulted in increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year).

To examine the assumption of equivalence between docetaxel and paclitaxel, the ERG performed a threshold analysis (conditional on the deterministic ERG base-case). This analysis indicated that if paclitaxel is more effective than docetaxel in terms of OS and PFS, up to a HR of approximately 0.93, nivolumab would not be cost effective compared with paclitaxel (assuming a threshold of £50,000 per QALY). Additionally, the cost effectiveness of nivolumab versus paclitaxel is uncertain given, as stated in Section 1.3, there is some evidence, albeit weak, that paclitaxel is possibly more effective than nivolumab.

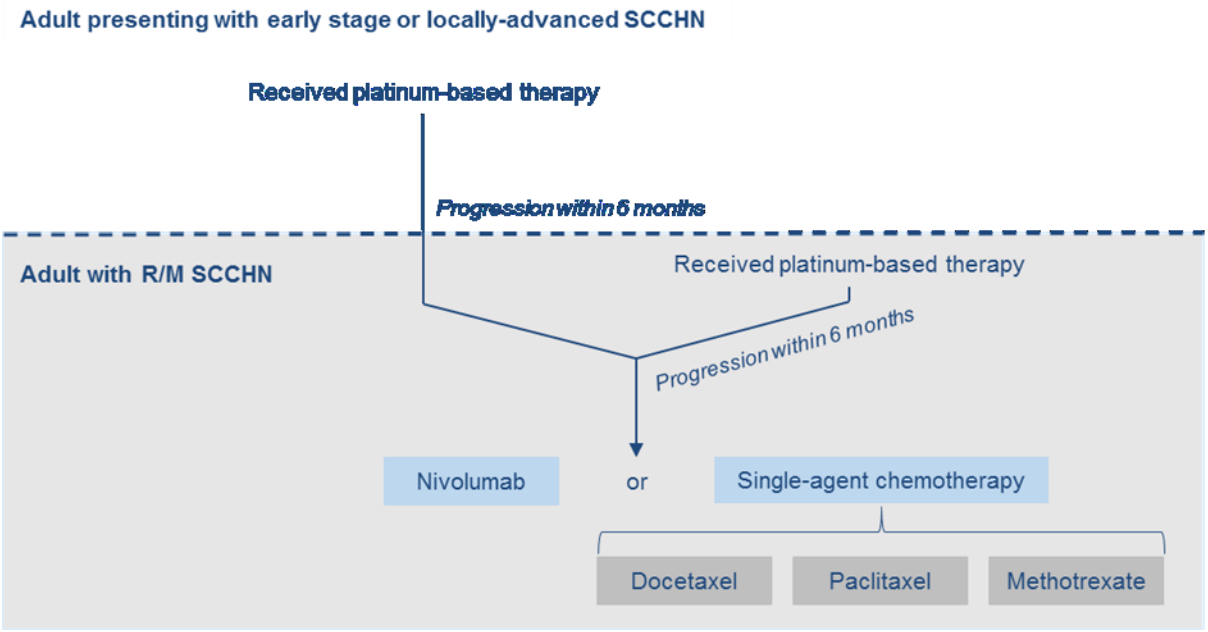
2. BACKGROUND

2.1 Critique of company's description of underlying health problem.

The company submission (CS) in Section 3.1 states that head and neck cancer is a broad term for cancers that arise from several anatomical locations within the head and neck region.[1] It excludes tumours of the brain and related tissues.[2] Irrespective of precise anatomical location, more than 90% of all malignant tumours are squamous cell carcinomas of the head and neck (SCCHN).[3] They arise from the lining mucosa, although the most common sites of tumours are the mouth (oral cavity), voice box (larynx) and the pharynx (consisting of the nasopharynx, oropharynx and hypopharynx).[4]

Of those presenting with SCCHN, up to 20–30% of patients go on to develop local and/or regional recurrences and distant metastases.[5] Around 4% of patients in the United Kingdom (UK) will present with metastatic disease.[6] The population in the scope is those patients with relapsed or metastatic disease (R/M SCCHN) who have progressed after receiving platinum-based chemotherapy.[7] As the company point out, this could be at one of two main stages in the disease, before or after progression to R/M SCCHN (Figure 2.1).[1]

Figure 2.1: Clinical care pathway for adults with R/M SCCHN who have progressed after platinum-based therapy



Source: Based on Figure 6 of the CS[1]
CS = company submission; R/M SCCHN = relapsed or metastatic squamous cell carcinoma of the head and neck

ERG comment: The ERG considers the description of the underlying health problem to be in line with that presented in the scope issued by the National Institute for Health and Care Excellence (NICE).[7]

2.2 Critique of company's overview of current service provision

The CS states that there is no standard therapy for R/M SCCHN and that this is reflected in the lack of recommendations by the British Association of Head and Neck Oncologists (BAHNO) and the European Head and Neck Society-European Society of Medical Oncologists-European Society for Radiotherapy and Oncology (EHNS-ESMO-ESTRO, 2010) Guidelines Working Group.[3, 8] As stated in Section 2.1, patients should be eligible for nivolumab at one of two main stages in the disease, before or after progression to R/M SCCHN (Figure 2.1).[1]

ERG comment: In Section 6.1 of the CS where the prevalence of the population eligible for nivolumab is calculated, it appears from Figure 58 that patients who progress following platinum-based chemotherapy for R/M disease have to have received platinum-based chemoradiotherapy before progression to R/M disease.[1] This figure appears to be based on the evidence of only one clinical expert.[9] It is therefore not clear why patients who progress following platinum-based chemotherapy cannot be eligible for nivolumab if they have received non-platinum-based chemoradiotherapy pre-R/M disease.

The ERG requested clarification (Question A4)[10] and the company replied that *"...the 7% of patients who were not eligible for platinum-based chemoradiotherapy in the locally-advanced setting would either a) be unable to tolerate (i.e. contra-indicated) platinum-based therapy, b) not be fit enough to receive platinum-based therapy, or c) simply not wish to receive platinum-based chemoradiotherapy (...) Given that these patients are platinum-ineligible in the locally-advanced setting it is very unlikely that they would go on to receive platinum-based chemotherapy at later stages of disease (i.e. in R/M disease)".*[11]

This seems to be a plausible explanation. The ERG verified that lack of standard care in R/M SCCHN generally is indeed the case and continues to be in the latest BAHNO guidelines. Page S73 reads: *"Chemotherapy or targeted biological agents may be indicated for patients with recurrent and/or metastatic disease but prognosis for patients with metastatic disease has a median survival of approximately 6–12 months in most studies"*:[12]

In the section on distant metastases (page S73), the guideline states that the most common regimens involve platinum, either cisplatin or carboplatin with 5-FU (5-Fluoruracil).[12] In the chapter on recurrence (page S181), the guideline goes on to state that *"patients with recurrence should be assessed systematically by a team experienced in the range of management options available for recurrence including surgical salvage, re-irradiation, chemotherapy and palliative care".*[12] The options for chemotherapy depend on performance status and fitness, but always include platinum in combination either with cetuximab or 5-FU for the less fit or with both for the fitter.[12]

The BAHNO guidance (page S187) also reveals that there is no standard care following progression on platinum therapy in R/M patients: *"Once patients have progressed on platinum based chemotherapy, the prognosis is extremely poor and there is no standard second-line or third-line therapy for these patients".*[12]

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with R/M SCCHN who have previously received platinum-based chemotherapy.	Adults with R/M SCCHN who have previously received platinum-based chemotherapy.	N/A – the decision problem matches the final scope
Intervention	Nivolumab	Nivolumab	N/A – the decision problem matches the final scope
Comparator(s)	• Docetaxel • Paclitaxel • Methotrexate	• Docetaxel • Paclitaxel • Methotrexate	N/A – the decision problem matches the final scope
Outcomes	• Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	N/A – the decision problem matches the final scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	The economic analysis is consistent with the final scope, presenting results in terms of incremental cost per QALY and using an appropriate time horizon of 20 years. The perspective of the analysis was that of the NHS and PSS.	N/A – the decision problem matches the final scope
Subgroups to be considered	None detailed	N/A	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	None detailed	N/A	N/A

Source: Based on Table 2 of the CS[1]

CS = company submission; IC = investigator's choice; N/A =not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PSS = Personal Social Services; QALY = quality-adjusted life year; R/M = recurrent or metastatic; SCCHN = squamous-cell carcinoma of the head and neck

According to the CS, *"an application for a marketing authorisation in Europe for the indication detailed in this submission was submitted to the EMA on* [redacted] *and a positive opinion from the CHMP is anticipated on* [redacted] *".*

3.1 Population

As stated in Table 1 in the CS, the anticipated indication for nivolumab as a treatment for SCCHN is: *"Nivolumab (Opdivo®) is indicated for the treatment of recurrent or metastatic squamous-cell cancer of the head and neck after platinum-based therapy in adults".*[1]

ERG comment: This is precisely the population in the scope issued by NICE.[7] However, there seems to be a mismatch between this and the main trial, CheckMate 141.[13].

As stated in Table 9 in the CS, one of the inclusion criteria in the trial is the following: *'Tumour progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (i.e. with radiation after surgery), primary (i.e. with radiation), recurrent, or metastatic setting.'*[1] This would imply exclusion of those who have progressed after six months, although this contradicts the CS where Figure 63 appears to show that patients are only eligible after receipt of a first line of platinum-based therapy for R/M disease if progression occurs after six months (and not within six months).[1]

The company was asked to explain this discrepancy in the clarification letter (Question A5).[10] In response, they explained that *"...it is likely that patients who have progressed after 6 months of receiving platinum-based therapy may then be re-treated with platinum-based therapy prior to receiving further systemic anti-cancer therapy. By stipulating in the inclusion criteria that patients must have progressed within 6 months of the last dose of platinum-based therapy, the CheckMate 141 trial included those patients for whom platinum-based therapy was no longer an option – i.e., patients with R/M SCCHN after platinum-based therapy. The trial population is therefore consistent with the expected marketing authorisation for nivolumab and the scope for this appraisal and reflects the patient population that is expected to receive nivolumab in clinical practice".*[11]

The ERG therefore interprets this to mean that the company believes that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy.

3.2 Intervention

The intervention in the CS is nivolumab (Opdivo®).

ERG comment: The intervention matches the scope issued by NICE.[7]

3.3 Comparators

The comparators listed in the decision problem (Table 3.1) are in accordance with the NICE scope and they are those that are compared in the cost effectiveness analysis (CEA).[1]

ERG comment: There were several deviations from the scope in the clinical effectiveness section.

- Firstly, the company provided no evidence as to the effectiveness of paclitaxel. They were asked to present a review of five studies of paclitaxel that met the inclusion criteria for their systematic review in the clarification letter (Question A9).[10] The company response is presented in Section 4.3.
- Secondly, the main trial randomised patients either to nivolumab or to an *"investigator choice"* arm, which allowed clinicians to decide which of three treatments to prescribe thus preventing an ITT analysis of nivolumab versus any of the comparators.[1]
- Thirdly, IC in the main trial also included cetuximab, which is not within scope. In the clarification letter (Question A1), the company was asked to conduct all analyses excluding

cetuximab patients.[10] Their response is presented in Section 4.2.1 below. They were also asked (Question B2) to conduct survival analyses to inform the CEA by stratifying for treatment in order to provide estimates for each of the treatments in the scope i.e. docetaxel and methotrexate. Their response is presented in Section 5.2.6.

3.4 Outcomes

The NICE scope defined overall survival, progression-free survival, adverse effects of treatment and health-related quality of life as outcomes of interest.[7] These outcomes were addressed in the CS.[1]

ERG comment: The outcomes match the scope.

3.5 Other relevant factors

There is a Patient Access Scheme, which involves a [redacted] discount.

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[14] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[15] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of the clinical effectiveness search can be found in Appendix 1.

Clinical effectiveness

The CS states that a systematic review was conducted to identify evidence on the efficacy and safety of nivolumab for the treatment of platinum-refractory recurrent or metastatic squamous cell carcinoma (SCC) of the head and neck (Section 4.1).

Searches were reported for MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Methodology Register (CMR). The original searches were undertaken in November 2015, and the Embase and MEDLINE searches were conducted in tandem via the Embase.com Elsevier interface. Update searches were carried out during June and July 2016, and the Embase and MEDLINE components were searched simultaneously via the Ovid interface. Using Ovid for the update search required significant translation from the original Embase.com search syntax. The MEDLINE update search via Ovid also included e-Pub Ahead of Print, In-Process and other Non-Indexed Citations, and the MEDLINE Daily Update sections.

A supplementary PubMed search to identify in-process records and e-Pubs ahead of print was carried out during November 2015. As additional sections of MEDLINE were included in the 2016 update searches, the updated PubMed search was amended to retrieve records tagged as 'pubstatusaheadofprint' only. The CS reported searches of 2013-2015 conference proceedings to identify conference abstracts for the annual meetings of the American Health and Neck Society (AHNS), American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO). The conference proceedings were searched again for the update to include 2016 abstracts.

These meet the requirements detailed in the NICE guide to the methods of technology appraisal.[16]

Search strategies for the database searches were provided in the Appendix 3 of the CS[13] and were well reported and the majority of the strategies were reproducible. The ERG was not able to reproduce searches conducted in Embase.com.

For the most part, the database searches were clearly structured and divided into population and intervention facets. The strategies used combinations of index terms appropriate to the resource searched, free text and a number of synonyms for the condition, intervention and comparators. The host provider for each database was listed, and the specific dates the searches were conducted were provided. The date spans were not provided for all searches. Study design limits to identify RCTs and non-RCTs were applied. The study design filters were not referenced, so it was unclear whether the filters used were published objectively derived filters. The filters contained a combination of subject heading terms and free text terms and the ERG deemed them to be adequate.

For the original systematic literature review (SLR), the company searched Embase and MEDLINE simultaneously using a single database provider (Embase.com) and search strategy. This approach has limitations when using subject heading terms which could affect recall of results. Embase subject heading terms (Emtree) were used in the search strategy, and although simultaneous searching of

embase.com should automatically identify and search for equivalent MEDLINE subject heading terms (MeSH), it is not clear if this is the case for all potentially useful MeSH terms. Given the potential limitations of this approach, the ERG considered it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in the search strategy.

Embase and various MEDLINE sections were also searched simultaneously via Ovid for the update search. The update strategy appeared to contain free-text phrases and only Emtree indexing terms without MeSH equivalents. As observed with the Embase.com search, the combined approach may have limited comprehensiveness of the search strategy and impaired recall. Conducting separate searches of MEDLINE and Embase, using appropriate MeSH and Emtree respectively, may have mitigated this problem.

The ERG noted two major areas of concern when appraising the company's clinical effectiveness searches.

- Firstly, the update search differed substantially from the original SLR search, as different database hosts were used to access the databases for each search. This necessitated a translation of the Embase/MEDLINE strategy, resulting in unavoidable differences in the way the update strategy performed. The ERG was primarily concerned that the original strategy contained far fewer terms for the intervention and comparators than the update search.

  An explanation for the differences between the two strategies was provided briefly in the CS,[1] and more extensively in the clarification response.[11]

  Whilst the ERG appreciated that attempts were made to include free-text word variants and synonyms for the disease and interventions in the Ovid update search, concerns remain that the update search of 2015 appeared more sensitive and comprehensive than the original Embase.com strategy. The company strategy consisted of a single line for all the drug interventions (line 42, page 9)[13] which relied entirely on Embase.com's in-built synonym searching feature. For the Ovid update translation, 39 lines of indexing and free-text terms were used to perform the same function.

  As the ERG did not have access to the Embase.com host to test the implications for these differences, we are unable to comment on how well the synonym searching performed. For this reason, the ERG asked for clarification how the company ensured that the original strategy was equally sensitive when compared to the update strategy.[11]

  In the clarification response,[11] the company stated they are satisfied that the original search strategy was validated against the trials retrieved by recently conducted systematic reviews including Vermorken 2010 and Suh 2014. It is unclear whether the referenced Vermorken publication[5] is a systematic review, as it did not report any systematic review methods or search strategy used to identify those included references. Therefore the ERG did not consider this explanation sufficient to consider the CS strategy as validated. As no bibliographical reference was provided for Suh 2014 either in the clarification response[11] or the original CS,[1] the ERG was unable to comment on this response.

  Despite this explanation, the ERG still has concerns regarding the reliance on the Embase.com synonym function and the apparent differences between the original and update strategies.

- Secondly, the ERG was concerned that limiting the MEDLINE and Embase clinical and cost effectiveness searches to English language may have introduced potential language bias. Current best practice states that *"Whenever possible review authors should attempt to identify*

and assess for eligibility all possibly relevant reports of trials irrespective of language of publication".[17]

During the clarification process, the ERG queried the rationale for applying an English language limit to the Embase/MEDLINE clinical and cost effectiveness searches. The company responded that they consider the impact of this language restriction to be minimal, based on the Cochrane Handbook. The clarification response also cited *"Morrison et al."* in this justification. As no bibliographical reference was provided for *"Morrison et al."*, the ERG identified two potentially relevant publications by Morrison, published in 2009[18] and 2012,[19] which the company may have been referring to. Although Morrison[18] found no empirical evidence that exclusion of papers in languages other than English (LOE) lead to biased estimates of intervention effectiveness, their findings did not rule out *"the potential introduction of language bias when language restrictions [were] used"*.[18] Morrison's conclusions go on to *recommend "systematic reviewers of conventional medicine who hope to minimize the risk of producing a biased summary effect estimate should search for foreign language"*.[18]

The ERG remains concerned that the blanket English language restrictions applied to Embase and MEDLINE searches were too restrictive and not in line with current best practice.[17, 18, 20-23]

The ERG noted that restricting the results of the MEDLINE/Embase update search for English language only removed 2,192 records. It is unclear whether omitted papers would have been relevant, however the ERG believed potential language bias could have been avoided by removing the language restriction from the search strategy. Subsequently, the additional references could have been assessed for eligibility irrespective of language, and considered for translation on a case-by-case basis. If translation was not possible at that point, the exclusion of the references could have been clearly documented in the PRISMA flowchart in a more transparent manner.

As the ERG was unable to fully investigate the limitations discussed above and concerns remain, the clinical effectiveness searching was not considered adequate.

Indirect and mixed treatment comparisons

The clinical effectiveness searches reported in Section 4.1 and Appendix 1 included a facet of relevant comparators. However in Section 1.3,[1] the CS stated that *"indirect comparisons between comparators included in this appraisal (and versus nivolumab) were therefore not considered possible due to insufficient clinical trial data"*.

Non-randomised and non-controlled evidence

The clinical effectiveness searches reported in Section 4.1 and Appendix 1 were used to inform this section, and multiple study designs were included in the methodological search filter. The same limitations noted in the clinical effectiveness searches also applied in this context.

Adverse events

Separate adverse events (AE) searches were not performed. When the ERG queried this omission, the clarification response[11] stated that the clinical effectiveness searches reported in Section 4.1 and Appendix 1 were used to identify studies reporting safety data. The clinical effectiveness searches incorporated a methodological filter intended to limit the search to specific study designs, namely randomised controlled trials (RCTs), non-RCTS, controlled clinical trials (CCTs) and observational studies. Guidance by the Centre for Reviews and Dissemination (CRD)[24] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design

limits used. Unfortunately the ERG was unable to undertake independent AE searches and review the results within the STA timeline, as this would be outside of the ERG remit.

Summary of searching

The searches in the CS were well documented and easily reproducible; searches were carried out in line with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4.[16] Significant differences were noted between the original clinical effectiveness strategy and that used for the 2015 update. The MEDLINE and Embase searches were limited to English language only, which may have introduced a language bias. Separate adverse events searches were not conducted.

4.1.2 Inclusion criteria

The eligibility criteria for the systematic review of effectiveness are shown in Table 4.1.[1]

Table 4.1: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Description	Justification
Inclusion criteria		
Population	• Adult patients (≥18 years) of any race and gender • At least 80% of patients were required to have been clinically diagnosed with advanced/ metastatic (stage III/IV) SCCHN • At least 80% of patients were required to be platinum-experienced • Studies which assessed a mixed population were included only if subgroup data for the relevant population were reported	Consistent with final scope
Interventions	Any approved or investigational intervention, including: • Nivolumab, docetaxel, methotrexate, fluorouracil, bleomycin, cisplatin, cetuximab, temoporfin, cabazitaxel, irinotecan, afatinib, zalutumumab, gefitinib, carboplatin, paclitaxel, lapatinib, bevacizumab, panitumumab, nimotuzumab, capecitabine, erlotinib, canertinib, MPDL3280A, sorafenib, axitinib, buparlisib, MK-1775, pembrolizumab, MEDI4736, oxaliplatin, epirubicin, gemcitabine, vinorelbine, ifosfamide, pemetrexed, advexin, regorafenib • Combinations of any of the included interventions with a non-included intervention were also included.	Consistent with final scope
Outcomes	• Any efficacy outcomes • Any safety outcomes	Consistent with final scope
Study design	• Randomised controlled trials, including those with cross-over or parallel group designs • Non-randomised controlled trials • Single-arm, uncontrolled trials • Retrospective or prospective cohort studies • Case-control studies • Cross-sectional studies • Analyses of hospital records/databases	None given

	Description	Justification
	• Systematic reviews or meta-analyses of relevant studies were included at the title and abstract screening stage for the purpose of identifying any additional studies not identified in the database searches, but were excluded at the full-text screening stage	
Language restrictions	English language only	None given
Exclusion criteria		
Population	• Studies focusing on children or adolescents were excluded • Studies where patients were platinum-naïve, or platinum status was unclear were excluded	As specified by final scope
Interventions	• Interventions not listed in the inclusion criteria, including radiotherapy, surgery and chemo-radiotherapy	Not relevant to final scope
Outcomes	N/A	N/A
Study design	• Case studies • Case series • Case reports	None given
Language restrictions	N/A	N/A

Source: Table 6 of the CS[1]
CS = company submission; N/A = not applicable; SCCHN = squamous cell carcinoma of the head and neck; SLR = systematic literature review

ERG comment: The ERG considers that these criteria were consistent with the scope.[7]

4.1.3 Critique of data extraction

The company identified 77 studies that studied at least one of the comparators and these were listed in Appendix 2 of the CS.[13] The company report that only one study was included, which is the CheckMate 141 trial because it was the only one that reported the efficacy of nivolumab.[1]

The company did not specify which data were extracted for reporting in the CS from the CheckMate 141 trial or how many reviewers were involved in the data extraction process. However, the company have provided a full CSR for the CheckMate 141 trial.[25]

ERG comment: The ERG checked the 118 articles identified in the original and updated systematic review and screened in full text.[13] As stated in the CS, only CheckMate 141 reports on the efficacy of nivolumab. In addition, no relevant studies for a potential network meta-analysis were identified.

It should be noted that the lack of a second reviewer in systematic reviews, i.e. in data extraction process, can increase the risk of bias and error in the review.

4.1.4 Quality assessment

Quality assessment was only carried out on the only included study i.e. the CheckMate 141 trial, which is shown in Table 4.2 (Table 14 in the CS).[1]

Table 4.2: Quality assessment results for CheckMate 141

Question	CheckMate 141	
	Response	**Justification for response**
Was randomisation carried out appropriately?	Yes	Randomisation was conducted using a centralised IVRS
Was the concealment of treatment allocation adequate?	No	The intended IC of therapy was entered in the IVRS for all patients prior to randomisation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline demographics and disease characteristics were generally well-balanced between treatment groups (see Section 4.5 of the CS)
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	CheckMate 141 was an open-label study
Were there any unexpected imbalances in drop‑outs between groups?	No	A higher proportion of patients in the IC arm (97.3%) did not continue with study treatment compared to the nivolumab arm (82.6%). However, the majority of discontinuations were due to disease progression (70.6%) or study drug toxicity (5.8%), which were both greater in the IC arm (see Section 4.5 of the CS), and are both expected reasons for discontinuation. A higher proportion of randomised patients did not receive treatment in the IC arm (8.3%) than the nivolumab arm (1.7%). Given that the main reason for randomised patients in the IC arm not receiving study treatment was withdrawal of consent, this may reflect the open-label nature of the trial and the fact that patients did not want to proceed with the trial upon finding they had been randomised to IC of therapy.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All primary and secondary endpoints listed have been reported in the CSR (7th June 2016)
Did the analysis include an intention‑to‑treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Analyses of efficacy outcomes, including the primary endpoint, were conducted in the all-randomised population. For time to event outcomes, appropriate censoring methods were used (see Section 4.4 of the CS).

Source: Based on Table 14 of the CS[1]

Note: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).[24] These results were based on an appraisal of CheckMate 141 using the CheckMate 141 CSR (7th June 2016)[25]

CRD = Centre for Reviews and Dissemination; CS = company submission; CSR = Clinical Study Report; IC = investigator's choice; IVRS = interactive voice response system.

ERG comment: The ERG agrees with the quality assessment except in one respect, which is allocation concealment. The ERG finds that the fact that the IC was 'entered into' the interactive voice response system (IVRS) is no reason to prevent allocation concealment, which is in principle guaranteed by the use of an IVRS. However, it should be noted that the quality assessment of CheckMate 141 identified a few issues which might influence the validity of the findings, i.e. the lack of blinding as well as imbalances in the drop-outs between treatment and comparator. A more detailed discussion can be found in Section 4.2.1 of this report.

4.1.5 Evidence synthesis

Because only one trial was found that compared either nivolumab to any comparator or any comparator to any other comparator, evidence synthesis was not appropriate.[1] However, given that the CheckMate 141 trial did not include paclitaxel, the ERG did ask for a review of the five paclitaxel trials in order to test the assumption of equal effectiveness between docetaxel and paclitaxel.[11] Section 4.3 presents an overview of these studies and discusses their findings.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 CheckMate 141 trial

Design and baseline characteristics

The evidence base for the clinical efficacy of nivolumab in the treatment of SCCHN consists of one RCT.[1, 26, 27] The company report that only the CheckMate 141 trial was included because it was the only one that reported the efficacy of nivolumab.

CheckMate 141 was a phase III, multicentre randomised, open-label, active-controlled, parallel group trial comparing the efficacy and safety of nivolumab with IC, which included choice at the clinician's discretion of docetaxel, methotrexate or cetuximab. Its main methodological features are summarised in Table 4.3.[1]

Table 4.4 summarises the definitions of primary and secondary efficacy outcomes, provided in Section 4.3.3 of the CS.[1] The demographics and baseline characteristics of participants of the CheckMate 141 trial are summarised in Table 4.5.[1] There is a problem with comparing baseline characteristics between the nivolumab and the other arm in the trial in that the other arm is composite of three other treatments and so the table from Appendix 4 of the CS is also presented in Table 4.5.[13]

Table 4.3: Summary of CheckMate 141 trial methodology

Trial name	CheckMate 141
Location	International: 55 study sites across 15 countries in North America (USA and Canada), South America, Europe and Asia[25] Five study sites were included in the UK, with a total of 34 patients randomised to study treatment at UK sites[25]
Trial design	Multicentre, open-label, phase III randomised controlled trial
Method of randomisation	Patients were randomised (2:1) to receive either nivolumab or IC of therapy, with stratification by prior cetuximab treatment (yes or no). Randomisation was conducted using a centralised IVRS. The investigator's intended choice of therapy (docetaxel, methotrexate or cetuximab) was entered in the IVRS for every patient prior to randomisation.

Trial name	CheckMate 141
Eligibility criteria for participants	*Key inclusion criteria:* • Males and females ≥18 years of age with an ECOG performance status of 0 or 1 • Histologically confirmed R/M SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) • Tumour progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant, primary, recurrent, or metastatic setting • Measurable disease by CT or MRI per RECIST 1.1 criteria[28] • Documentation of p-16 positive or p-16 negative disease to determine HPV-p16 status of tumour for SCCHN of the oropharynx • Availability of tumour samples for PD-L1 expression analysis *Key exclusion criteria:* • Active, known or suspected autoimmune disease • Systemic treatment with either corticosteroids or other immunosuppressive medications (within 14 days of study drug administration) • Active brain metastases or leptomeningeal metastases • Histologically confirmed R/M carcinoma of the nasopharynx, SCC of unknown primary, and salivary gland or non-squamous histologies (e.g. mucosal melanoma) • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways A full list of inclusion and exclusion criteria is presented in Table 9 of the CS.[1]
Settings and locations where the data were collected	Data were collected in accordance with Good Clinical Practice by trained and qualified investigators using a single protocol to promote consistency across the multiple study sites. An independent DMC was established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio. The DMC acted in an advisory capacity to the study sponsor, monitoring patient safety and evaluating the available efficacy data for the study.
Trial drugs and method of administration	*Nivolumab group (n=240)* • Nivolumab, i.v. infusion, 3 mg/kg, Q2W Four patients randomised to the nivolumab arm did not receive ≥1 dose of study treatment. *Investigator's choice (n=121)* Patients were randomised to the IC arm and received one of the three possible therapies at the discretion of the investigator (see list below). Investigators were to indicate their intended choice of therapy for each patient prior to randomisation. • Docetaxel (30 mg/m^2, i.v. infusion, QW) (n=54)[a] • Methotrexate (40 mg/m^2, i.v. infusion, QW) (n=52)[b] • Cetuximab (400 mg/m^2, i.v. infusion, once, then 250 mg/m^2, i.v., QW) (n=15)[c] Ten patients randomised to the IC arm did not receive ≥1 dose of study treatment. Treatment in both arms was continued until progression, unacceptable toxicity, or withdrawal of consent. Patients in the nivolumab arm were permitted to continue treatment beyond investigator-assessed RECIST 1.1-defined

Trial name	CheckMate 141
	progression if they were experiencing a clinical benefit, as determined by the investigator, and were tolerating the study drug. Dose reductions were not permitted for nivolumab but were allowed for therapies in the IC arm. Dose delays were permitted in both trial arms.
Permitted and disallowed concomitant medication	The following medications were prohibited during the study: • Immunosuppressive agents (except to treat a drug-related adverse event) • Systemic corticosteroids >10 mg daily prednisone equivalent[d] • Any concurrent anti-neoplastic therapy Supportive care for disease-related symptoms was permitted for all patients in the trial. Surgical resection of solitary lesions and palliative radiotherapy were permitted during the trial if certain protocol-defined criteria were met.[25] Prior palliative radiotherapy must have been completed at least 2 weeks before study drug administration.
Primary outcomes	*Overall survival (OS)* Patients were followed up continuously whilst on study treatment and then every 3 months until death, loss to follow-up, or withdrawal of study consent after patients discontinued study treatment.
Secondary and other outcomes	*Secondary endpoints:* • Progression-free survival (PFS) • Objective response rate (ORR) *Exploratory endpoints:* • Duration of response (DOR) • Time to response (TTR) • Safety • Patient-reported outcomes (PROs) assessed using EORTC QLQ-C30 and QLQ-H&N35 questionnaires, as well as the EQ-5D-3L questionnaire A full description of outcomes is presented in Table 4.4. *Timing of assessments:* • Tumour assessments were scheduled every 6 weeks as of Week 9 until disease progression or treatment discontinuation (whichever occurred last). Assessments were performed using CT or MRI and included the head and neck, chest, abdomen and all known sites of disease. Changes in tumour responses were determined by the investigator and assessed according to RECIST 1.1.[28] • AEs were assessed during treatment visits and were included in safety analyses if they occurred within 30 days from the day of the last dose received. • HRQoL was assessed before each dose at Week 1, then every 6 weeks as of Week 9. Two follow-up visits and subsequent survival follow-up visits were also scheduled (AEs and PROs)[e]
Subgroups	A pre-planned exploratory subgroup analysis of OS by treatment group and PD-L1 expression (≥1% or <1%) was conducted. In addition, the following exploratory analyses were added after database lock to help further characterise the study results: • OS of nivolumab versus IC by HPV-p16 status (positive or negative) • OS of nivolumab versus IC by selected demographic and baseline characteristics, including intended therapy for the IC arm

Trial name	CheckMate 141
	Full details of subgroup analyses are presented in Section 4.8 of the CS.
Duration of study and follow-up	The study was initiated on the 29th May 2014 with the last patient last visit on 6th November 2015 and the clinical database locked on the 18th December 2015. At this data cut-off point, the median duration of follow-up was 5.3 months (range, 0.0–16.8) and 4.6 months (range, 0.0–15.2) in the nivolumab and IC arms, respectively.

Source: Based on Table 8 of the CS[1]

Notes: [a] Dose of docetaxel could be increased to 40 mg/m^2 if tolerated, as per local practices; [b] Dose of methotrexate could be increased to 60 mg/m^2 if tolerated, as per local practices; [c] Cetuximab was only administered where approved for use as a monotherapy for recurrent SCCHN; [d] Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents were permitted in the absence of active autoimmune disease; [e] Follow-Up Visit 1 was scheduled for 35 days from the last dose ±7 days or coincided with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose. Follow-Up Visit 2 was scheduled for 80 days (±7 days) from Follow-Up Visit 1. Survival follow-up visits were scheduled for every 3 months (± 7 days) from Follow-Up Visit 2.

AEs = adverse events; CS = company submission; CT = computerised tomography; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; DMC = Data Monitoring Committee; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 and H&N35 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and Head and Neck 35; EQ-5D-3L = 3-level EuroQoL 5-Dimensions; HPV = human papillomavirus; HRQoL = health-related quality of life; i.v. = intravenous; IC = investigator's choice; IDMC = independent data monitoring committee; IVRS = interactive voice response system; MRI = magnetic resonance imaging; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; PFS = progression-free survival; PROs = patient-reported outcomes; Q2W = once every two weeks; QW = once weekly; RECIST = Response Evaluation Criteria In Solid Tumours; R/M = recurrent or metastatic; SCC = squamous-cell carcinoma; SCCHN = squamous-cell carcinoma of the head and neck; TTR = time to response; UK = United Kingdom; USA = United States of America

Table 4.4: Description of outcomes reported in CheckMate 141

Outcome	Description and method of assessment
Primary	
Overall survival (OS)	OS was defined as the time from randomisation to the date of death from any cause. The survival time for patients who had not died was censored at the last known alive date. OS was censored at the date of randomisation for patients who were randomised but had no follow-up. Patients were followed up continuously whilst on study treatment and then every 3 months until death, loss to follow-up, or withdrawal of study consent after patients discontinued study treatment.
Secondary	
Progression-free survival (PFS)[a]	PFS was defined as the time from randomisation to first date of documented progression, as determined by the investigator (as per RECIST 1.1 criteria),[28] or to death due to any cause, whichever occurred first. • Patients who neither progressed nor died were censored on the date of their last tumour assessment on study • Patients who did not have any on-study tumour assessments and did not die were censored on their date of randomisation

Outcome	Description and method of assessment
	• Patients who received subsequent systemic anti-cancer therapy prior to progression were censored at the date of their last tumour assessment on or prior to secondary therapy
Objective response rate (ORR)[a]	ORR was defined as the proportion of randomised patients who achieved a best overall response (BOR) of complete response (CR) or partial response (PR), based on RECIST 1.1 criteria,[28] as per investigator assessment. BOR was defined as the best response designation, recorded between the date of randomisation and the date of progression, as assessed by the investigator per RECIST 1.1,[28] or the date of subsequent anti-cancer therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurred first. For patients who continued treatment beyond progression, the BOR was determined based on response assessments up to the time of initial RECIST 1.1 progression.[28]
Exploratory	
Duration of response (DOR)[a,b]	DOR was defined as the time between the date of first confirmed response (CR or PR) to the date of the first documented progression as determined by the investigator (per RECIST 1.1 criteria),[28] or death due to any cause, whichever occurred first. For patients who neither progressed nor died, the duration of response was censored at the same time they were censored for PFS. DOR was evaluated for responders (i.e. patients with confirmed CR or PR) only.
Time to response (TTR)[a]	TTR was defined as the time from randomisation to the date of the first response (CR or PR), as assessed by the investigator. TTR was evaluated for responders (i.e. patients with a BOR of confirmed CR or PR) only.
Safety	The assessment of safety was based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, and abnormalities in specific clinical laboratory assessments. 'Select' AE analyses included incidence, time-to-onset, and time-to-resolution. Analyses were conducted using the 30-day and 100-day safety window from day of last dose received. AEs were coded using the MedDRA Version 18.1. AEs and laboratory values were graded for severity according to the NCI CTCAE version 4.0.
EORTC QLQ-C30 and QLQ-H&N35	The *EORTC QLQ-C30* has 30 items divided among 5 functional scales (physical, role, emotional, social, and cognitive), 3 multi-item symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and 6 single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The two items measuring overall health status and quality of life are graded on a 7-point Likert scale, while all remaining items are graded on a 4-point scale: 1 (not at all) to 4 (very much). The *EORTC QLQ-H&N35* is a 35-item instrument grouped into 7 multi-item scales (pain, swallowing, sensory problems, speech problems, trouble with social eating, trouble with social contact, and reduced sexuality) and 11 single-item scales (teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, and weight gain). 30 items are graded on a 4-point scale and 5 items utilise a binary response set (yes/no).

Outcome	Description and method of assessment
	For each item, raw scores were transformed to a 0–100 scale with higher scale scores representing better functioning or HRQoL (functional and global health status/HRQoL scales) or worsening of symptoms (symptom scales). A clinically meaningful change in score was regarded as a change in ≥10 points.[29, 30]
EQ-5D	The *EQ-5D* is a standardised instrument used to measure self-reports of general health status. The *EQ-5D-3L* descriptive system is comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, moderate problems, and extreme health problems. The *EQ- 5D VAS* recorded the patient's self-rated health state on a 100-point vertical VAS (0 = worst imaginable health state; 100 = best imaginable health state). For the EQ-5D VAS, a change in seven points was regarded as clinically meaningful.[31]

Source: Based on Table 10 of the CS[1]

Notes: [a] The first on-study tumour assessment was scheduled at Week 9 (±1 week) following randomisation. Subsequent tumour assessments were scheduled every 6 weeks (±1 week) until disease progression; [b] DOR data were not available at the time of submission (see Section 4.14 of the CS)

AEs = adverse events; BOR = best overall response; CR = complete response; DOR = duration of response; EORTC QLQ-C30 and H&N35 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and Head and Neck 35; EQ-5D = European Quality of Life-5 Dimensions; EQ-5D-3L = 3-level EuroQoL 5-Dimensions; HRQoL = health-related quality of life; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumours; SAEs = serious adverse events; TTR = time to response; VAS = Visual Analogue Scale

Table 4.5: Baseline characteristics of patients in the all-randomised population in CheckMate 141 by individual therapy[a]

Characteristic	Nivolumab (n=240)	IC (n=121)	Docetaxel (n=54)	Methotrexate (n=52)	Cetuximab (n=15)
Demographics					
Age, median years (range)	59.0 (29–83)	61.0 (28–78)	[redacted]	[redacted]	[redacted]
Age categorisation, n (%)					
<65	172 (71.7)	76 (62.8)	[redacted]	[redacted]	[redacted]
≥65 and <75	56 (23.3)	39 (32.2)	[redacted]	[redacted]	[redacted]
≥75	12 (5.0)	6 (5.0)	[redacted]	[redacted]	[redacted]
Male, n (%)	197 (82.1)	103 (85.1)	[redacted]	[redacted]	[redacted]
Race, n (%)					
White	196 (81.7)	104 (86.0)	[redacted]	[redacted]	[redacted]
Black/African American	10 (4.2)	3 (2.5)	[redacted]	[redacted]	[redacted]
Asian	29 (12.1)	14 (11.6)	[redacted]	[redacted]	[redacted]
Other	5 (2.1)	0	[redacted]	[redacted]	[redacted]
Region, n (%)					
North America	101 (42.1)	44 (36.4)	[redacted]	[redacted]	[redacted]
Europe	109 (45.4)	62 (51.2)	[redacted]	[redacted]	[redacted]
Rest of the world	30 (12.5)	15 (12.4)	[redacted]	[redacted]	[redacted]
Tobacco use, n (%)					
Current/former	191 (79.6)	85 (70.2)	[redacted]	[redacted]	[redacted]
Never	39 (16.3)	31 (25.6)	[redacted]	[redacted]	[redacted]
Unknown	10 (4.2)	5 (4.1)	[redacted]	[redacted]	[redacted]
Disease characteristics					
Site of primary tumour, n (%)[b]					
Oral cavity	108 (45.0)	67 (55.4)	[redacted]	[redacted]	[redacted]

Characteristic	Nivolumab (n=240)	IC (n=121)	Docetaxel (n=54)	Methotrexate (n=52)	Cetuximab (n=15)
Pharynx	92 (38.3)	36 (29.8)	[redacted]	[redacted]	[redacted]
Larynx	34 (14.2)	15 (12.4)	[redacted]	[redacted]	[redacted]
Other	6 (2.5)	3 (2.5)	[redacted]	[redacted]	[redacted]
HPV p-16 status, n (%)					
Positive	63 (26.3)	29 (24.0)	[redacted]	[redacted]	[redacted]
Negative	50 (20.8)	36 (29.8)	[redacted]	[redacted]	[redacted]
Not tested[c]	127 (52.9)	56 (46.3)	[redacted]	[redacted]	[redacted]
Prior therapy					
Number of lines of prior systemic cancer therapy, n (%)					
1	106 (44.2)	58 (47.9)	[redacted]	[redacted]	[redacted]
2	80 (33.3)	45 (37.2)	[redacted]	[redacted]	[redacted]
≥3	54 (22.5)	18 (14.9)	[redacted]	[redacted]	[redacted]
ECOG PS (%)					
0	49 (20.4)	23 (19.0)	Not reported		
1	189 (78.8)	94 (77.7)			
≥ 2	1 (0.4)	3 (2.5)			
Not reported	1 (0.4)	1 (0.8)			

Source: CheckMate 141 CSR (7th June 2016) – Tables S.3.1a, S.3.3a and S.3.8a[25]

Notes: [a] The investigator had to indicate which IC agent he or she would use if the subject were randomised the IC arm. This information was recorded in the IVRS system prior to randomisation; [b] Each was not subcategorised to capture a more precise primary tumour site (e.g., oropharynx); [c] Baseline 'unknown' HPV status included 180 patients who were not tested (per protocol, HPV status testing was only required for patients with oropharyngeal disease), 2 patients whose sample was collected after baseline, and 1 nivolumab subject who was tested for HPV, but had a non-evaluable test result.

CSR = clinical study report; ECOG PS = Eastern Cooperative Oncology Group performance status; HPV= human papillomavirus; IC= investigator's choice; IVRS= interactive voice response system

ERG comment:

Patient characteristics

Baseline characteristics seem to be comparable between the two arms, although unsurprisingly, given the IC design, this is not the case between the various treatments (Table 4.5). For example, the percentage of patients who have received at least three lines of therapy is much higher for methotrexate than docetaxel.

There is also an issue of generalisability. According to page 30 of the CS, the ratio of males to females affected by SCCHN is 2.4:1, which would, assuming an equal mortality rate, imply a prevalence of approximately 70% male in the index population.[1] However, in the CheckMate 141 trial, 83.1% are male (Table 13 of the CS).[1] This discrepancy could have implications on the estimated effectiveness in that the CheckMate 141 clinical study report (CSR) shows a large difference due to gender. In Figure 7.2.1-1, the hazard ratio (HR) for OS of nivolumab versus individual investigator's choice therapies was 0.65 (95% confidence interval (CI) 0.48 to 0.88) for males and 0.93 (95% CI 0.47 to 1.85) for females.[25]

In the clarification letter (Question A6), the ERG asked the company to explain how the CheckMate 141 trial is representative of the population.[10] The company responded that the CS contained a mistake and that the ratio of males to females should be 2.24 and not 2.4.[11] However, the ERG estimates that this would make very little difference to prevalence and so the question would remain as to whether the trial is representative. On page 25 of the response to request for clarification, the company also stated that *"in other licensed indications, no concerns have been raised with regards to differing efficacy between males and females"*.[11]

However, the ERG would argue that this does not rule out there being a difference in efficacy in SCCHN. The company also responded that the CI for OS HR in females is wide and attribute this at least partly to the small number of females. Indeed the CI for females does overlap that for males. In conclusion, whilst there remain questions as to the gender ratio representativeness of the CheckMate 141 trial and about the consequences of any discrepancy, no firm conclusions can be drawn.

A further issue regarding generalisability regarded the inclusion of countries other than the UK. It was mentioned in the clarification letter (Question A7) by the ERG that there was a difference in the OS HRs between North America and the European Union (EU), i.e. 0.55 (95% CI 0.36 to 0.85) and 0.91 (95% CI 0.62 to 1.33), respectively.[10] The company responded by providing some evidence that might explain this difference.[11] This included the lower proportion of human papillomavirus (HPV)-positive and never smoker patients in Europe, an imbalance of HPV status across treatment arms within the European subgroup and differences in choice of IC of therapy. What seems to be clear is that there are differences both in the recorded baseline characteristics between the EU and North America and, perhaps more importantly, in the treatments chosen.

- Firstly, [redacted], which appears to be due to difference in clinical practice.
- Secondly, methotrexate was given to [redacted] patients in the EU versus [redacted] in North America.

Given that the underlying premise of IC is that treatments are intended to be given according to clinician judgement, it logically follows that the clinician is responding to some characteristics of the patient, whether recorded or not. Indeed, this is what the company states in the CS (page 32): *'The choice of therapy is often determined by the type of prior therapies received and overall patient fitness. For*

example, patients who have received prior treatment with a taxane will most likely receive methotrexate, as will patients with poor overall fitness and those who cannot tolerate docetaxel".[1]

It therefore follows that if [redacted] of EU patients would have been intended by their clinicians to receive methotrexate then [redacted] were the kind of patient who were believed by clinicians to require methotrexate (as opposed to docetaxel). It therefore appears that there were fewer of these kinds of patients [redacted] in the EU than in North America.

Quality

As shown in Table 4.2 above, the CheckMate 141 trial was lacking in quality in that it was open label and thus prone to bias. This was further compounded by the fact that clinicians were able to exercise their own judgment in both concomitant and treatment on progression (subsequent treatment). As it states in Table 4.3 above, surgery and radiotherapy were permitted. Indeed, rates of surgery and radiotherapy are reported as *"subsequent therapies"* in Appendix 3 and it is clear that a higher percentage of nivolumab patients received this (12.1% versus 9.9%).[13] The percentage who received subsequent systemic therapy was lower for nivolumab (29.6% versus 32.2%), but the percentage who received *"experimental drugs"* and taxanes was higher for nivolumab (3.8% versus 1.7% and 11.7% versus 8.3% respectively). In the clarification letter (Question A3), the company were asked to explain this and perform exploratory analyses to try to control for the effect of subsequent therapy.[10] Their response was that the CheckMate 141 trial did not give guidance to investigators on the choice of subsequent therapy.[11] The results of additional analyses are in Section 4.2.1.

Results of the study

The CheckMate 141 trial included the following outcome measures to assess the outcomes defined in the final scope (see Table 3.1):

- Overall survival
- Progression-free survival
- Health-related quality of life
- Adverse effects of treatment

These results are presented below. Efficacy analyses were performed using the ITT population. Evidence from the CheckMate 141 trial for each of these outcomes is presented below in separate tables.

Overall survival

An overview of clinical effectiveness results (OS and PFS) from CheckMate 141 for nivolumab and the total IC arm is presented in Table 4.6. The main clinical effectiveness results presented in the CS are for nivolumab versus the total IC comparator arm, reflecting the two randomisation groups of the CheckMate 141 trial. Where possible, results by agent for the IC arm are presented as well.

The primary endpoint for the CheckMate 141 trial was OS, which demonstrated a significant improvement in the nivolumab arm compared to the IC arm (HR, 0.70 [97.73% CI, 0.51 to 0.96]; stratified (by prior cetuximab use) log-rank test p-value = 0.0101). The company stated that this is equivalent to a 30% reduction in risk of death with nivolumab versus IC of therapy.[27]

At the time of the initial database lock (18 December 2015), median OS was higher in the nivolumab arm (7.5 months; 95% CI, 5.5 to 9.1) versus the IC arm (5.1 months; 95% CI 4.0 to 6.0), after a median follow-up of 5.3 months (range 0–16.8) and 4.6 months (range 0.0–15.2) for each treatment group, respectively.[27]

The Kaplan-Meier (KM) plot for OS is presented in Figure 4.1. The HR for OS of nivolumab versus individual investigator's choice therapies was

[redacted]

The nivolumab, cetuximab, and methotrexate Kaplan-Meier OS curves [redacted]

The nivolumab and docetaxel KM OS curves [redacted] after this time point.

The KM plot for OS by agent is presented in Figure 4.2.

ERG comment: It can be seen that nivolumab resulted in a statistically significant reduction in the hazard rate at the 5% level and even at a higher threshold of 2.27% with a HR of 0.70 versus IC. However, there appears to be some variation by individual therapy with nivolumab performing particularly well versus cetuximab (HR=[redacted]) as opposed to versus docetaxel (HR=[redacted]). Cetuximab is also not in the NICE scope and therefore, the ERG requested in the clarification letter (Question A1) that the analyses be repeated excluding the data for cetuximab.[10] In response, the company argued that this would break the randomisation.[11] However, the ERG would argue that, whilst this does introduce a bias, it is legitimate at least as for illustrative purposes in that an estimate of the treatment effect versus cetuximab has already introduced a bias if it is not a legitimate comparator. The company provides the results of the requested analysis in Table 5 of the clarification letter.[11] As expected, it showed no change in terms of statistical significance, but a [redacted] in the advantage of nivolumab versus IC from a HR (97.73% CI) of 0.70 (0.51, 0.96; p=0.03236) to [redacted].

The ERG also believes that it is legitimate to analyse the trial results by each of the intended treatments, docetaxel, methotrexate or cetuximab. By legitimate, the ERG means that it is informative but also that the treatment effect by intended treatment is an unbiased estimate of treatment effect and essentially constitutes a subgroup analysis as described in Figure 7.2.1-1 in the CSR.[25] On this basis, from a clinical effectiveness only perspective, it appears that nivolumab does reduce the mortality rate versus methotrexate but is it is doubtful that it does versus docetaxel. This is consistent with the overlap in confidence intervals for median survival. For completeness, the ERG also requested in the clarification letter (Question A2) that analyses be performed that were stratified for prior cetuximab therapy, given that this was done in the primary efficacy analysis, but not to produce the values in Figure 7.2.1-1.[10] The company reported the results of these analyses, which are not reproduced in the ERG report given their very close proximity with Figure 7.2.1-1.

The ERG was also concerned about the use of subsequent therapies and any imbalance between nivolumab and IC. In the clarification letter (Question A3), the ERG therefore requested an exploratory analysis with simple censoring of any patient who had received subsequent systemic cancer therapy.[10] The company performed this analysis, the results of which were that the HR of death for nivolumab versus IC ([redacted]) were very similar to that observed in the primary analysis of OS (0.70; 0.51, 0.96), suggesting that the treatment effect of nivolumab versus IC is not affected by the type or timing of subsequent systemic therapy received in each treatment arm.[11] The ERG also requested a more sophisticated analysis to control for informed censoring such as inverse probability of censoring weights (IPCW), as recommended in the NICE Decision Support Unit Technical Support Document 16.[32] The company declined to do this, citing lack of time as the reason, although its need is probably to a large extent negated given the results of the naïve analysis, which showed that the treatment effect was the same whether with censoring or without.

One further point is that the claim of a 30% reduction in the risk of death is misleading since it seems to be predicated on treating the HR like a relative risk, which it is not. Indeed since the hazard rate is

bounded by zero and infinity, the HR is similarly bounded (excepting the implausible scenario of a rate of zero). On the other hand, the relative risk is defined as the ratio of probabilities, each of which is bounded by zero and one. What is more correct is to say that there is a 30% reduction in the mortality *rate*. In fact, one can calculate the relative risk of death at one year from Table 4.6, which is (100-36)/(100-16.6) i.e. 0.77. This implies a 23% reduction in the risk of death at one year.

Table 4.6: Overview of clinical effectiveness results from CheckMate 141 – all-randomised population

Outcome[a]	Nivolumab (n=240)	IC (n=121)	Methotrexate (n=52)	Docetaxel (n=54)	Cetuximab (n=15)
Overall Survival					
Deaths, n (%)	133 (55.4)	85 (70.2)	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)	[redacted]	[redacted]	[redacted]
HR for death with nivolumab (97.73% CI; p-value)[b]	0.70 (0.51, 0.96; p=0.0101)		0.64 (0.43, 0.96)[c] [redacted]	0.82 (0.53, 1.28)[c] [redacted]	0.47 (0.22, 1.101)[c] [redacted]
1-year survival rate, % (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)			
Progression-free survival[e]					
Events, n (%)	190 (79.2)	103 (85.1)	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	2.0 (1.9, 2.1)	2.3 (1.9, 3.1)	[redacted]	[redacted]	[redacted]
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)		[redacted]	[redacted]	[redacted]
6-month PFS rate, % (95% CI)	19.7 (14.6, 25.4)	9.9 (5.0, 16.9)			

Source: Gillison 2016[27], Ferris 2016[26] and CheckMate 141 CSR (7th June 2016)[25]

Notes: [a] Results are presented from the initial database lock of 18th December 2015 for OS and from the database lock of 5th May 2016 for PFS and tumour response; [b] The pre-specified boundary for statistical significance required the p-value to be less than 0.0227, 95% CI were 0.53, 0.92; [c] Reported in CS (intended IC): Figure 17, page 71; [d] Reported in CSR (actual treatment): Figure 7.2-2, page 82 (See also Figure 4.2 below). [e] Disease progression and tumour response were assessed by the investigator using RECIST version 1.1[28]; [f] Reported in CSR (intended IC): Figure 7.3.1-1, page 89

CI = confidence intervals; CS = company submission; CSR = clinical study report; HR = hazard ratio; IVRS = interactive voice response system; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours; TTR = time to response

Progression-free survival

There was no statistically significant difference in PFS (primary definition) between the nivolumab and investigator's choice groups (HR, 0.89; 95% CI, 0.70 to 1.1; p=0.3236) (based on events up to the database lock of 18 December 2015).[33] In addition, median PFS was less prolonged in the nivolumab arm (2.0 months [95% CI, 1.9 to 2.1] for nivolumab versus 2.3 months [95% CI, 1.9, 3.1] for IC of therapy).

As shown in Figure 4.3, there was delayed separation of the Kaplan-Meier curves in favour of nivolumab and by six months the PFS rate was higher in the nivolumab arm (19.7% [95% CI, 14.6 to 25.4]) compared to the IC arm (9.9% [95% CI, 5.0 to 16.9]).[33]

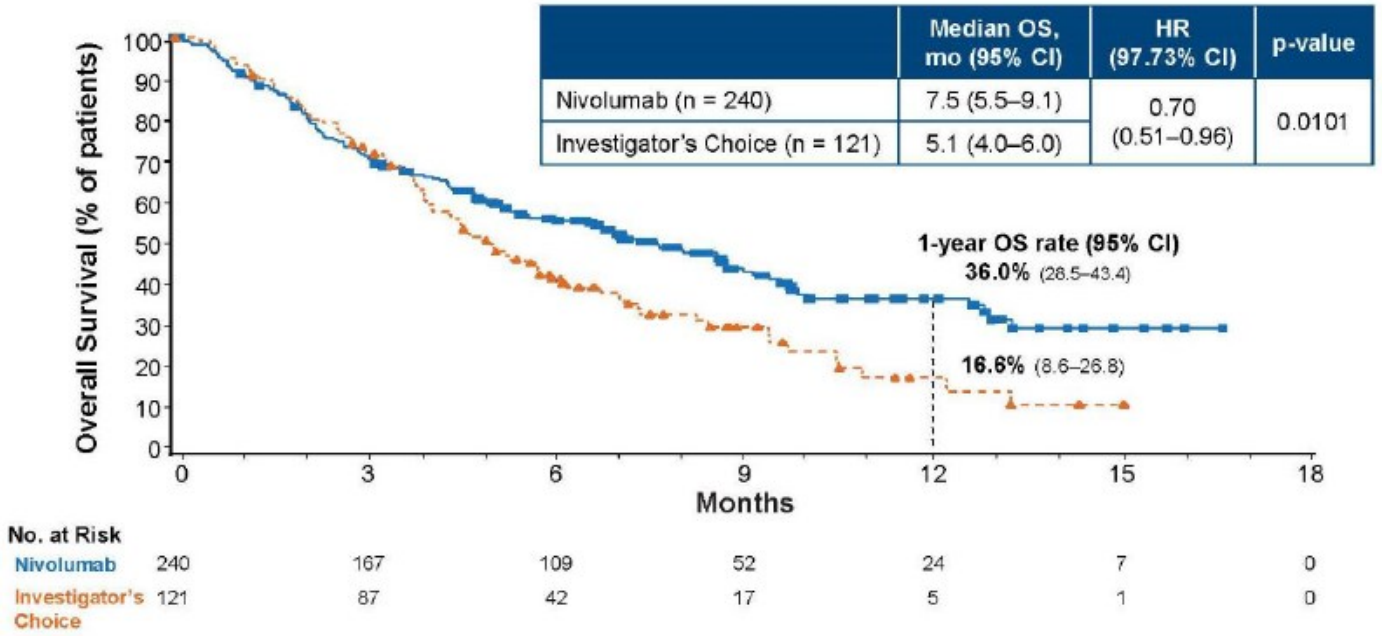
As with OS, results were provided for PFS in response to the clarification questions to exclude cetuximab.[10, 11]

[redacted]

Objective response rate

The objective response rate (ORR) was greater, albeit not statistically significantly, for nivolumab versus IC of therapy (13.3% [95% CI, 9.3% to 18.3%] versus 5.8% [95% CI, [2.4% to 11.6%]), with a higher proportion of patients in the nivolumab arm achieving a best overall response of either a complete or partial response, as compared to the IC arm. The median time to response (TTR) was similar in both treatment arms (2.1 months [range, 1.8–7.4] with nivolumab versus 2.0 months [range, 1.9–4.6] with IC of therapy]).

Figure 4.1: Kaplan-Meier plot for overall survival in the all-randomised population in CheckMate 141

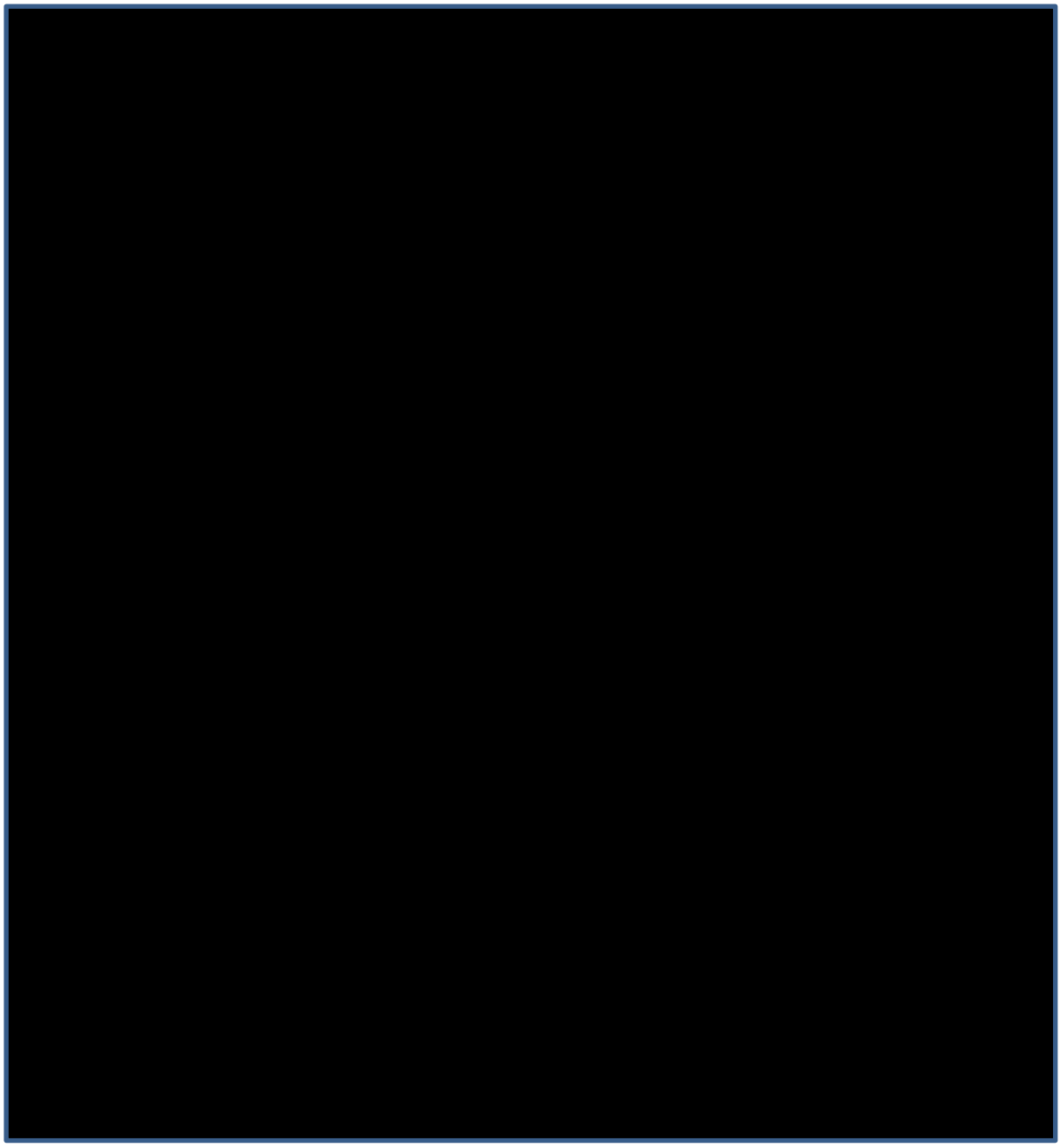


Source: Gillison 2016[27]

Note: The pre-specified boundary for statistical significance required the p-value to be less than 0.0227; 95% CI were 0.53, 0.92. The HR was computed using a stratified Cox proportional hazards model and the p-value was from a stratified log-rank test. Database lock of 18 December 2015.

CI = confidence intervals; HR = hazard ratio; OS = overall survival

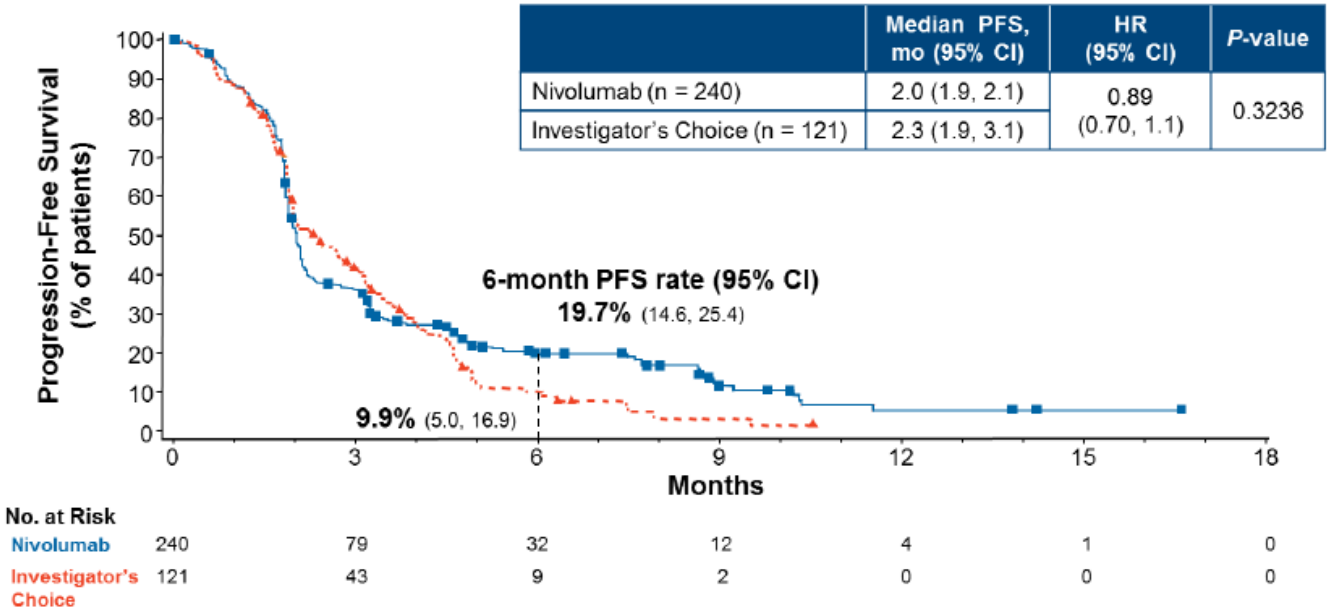
Figure 4.2: Kaplan-Meier overall survival plot by cetuximab, methotrexate, or docetaxel) - all randomised subjects



Source: CSR, Figure 7.2-2, page 82[25]
Notes: Symbols represent censored observations. Hazard ratio is based on unstratified Cox proportional hazards model with regimen – nivolumab, cetuximab, methotrexate or docetaxel - as the sole covariate.
CI = confidence interval; CSR = clinical study report; HR = hazard ratio

The number of patients that had experienced a PFS event by the time of the database lock was 190 (79.2%) in the nivolumab arm and 103 (85.1%) in the IC arm.[25, 28] In total, 139 and 71 patients in the nivolumab and IC arms, respectively, had experienced disease progression, assessed using RECIST version 1.1, as the PFS-defining event, and 51 and 32 patients in each arm had died prior to experiencing disease progression.[25]

Figure 4.3: Kaplan-Meier plot for progression-free survival in the all-randomised population in CheckMate 141



	Median PFS, mo (95% CI)	HR (95% CI)	*P*-value
Nivolumab (n = 240)	2.0 (1.9, 2.1)	0.89 (0.70, 1.1)	0.3236
Investigator's Choice (n = 121)	2.3 (1.9, 3.1)		

Source: Ferris 2016[26]

Note: Disease progression was assessed by the investigator using RECIST version 1.1.[28] The HR was computed using a stratified Cox proportional hazards model and the p-value was from a stratified log-rank test. Since death information was not updated for the latest database lock, and since PFS depends on both progression and death, PFS analyses were restricted to progression events (deaths or radiographic progressions) prior to the initial database lock of 18 December 2015.

CI = confidence intervals; HR = hazard ratio; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours.

Health-related quality of life

The CS and CSR report three QoL instruments: the EORTC General Cancer Module (QLQ-C30), the EORTC Head and Neck Specific Module (QLQ-H&N35) and the European Quality of Life questionnaire (EQ-5D).

The EORTC QLQ-C30[34] is the most commonly used quality-of-life instrument in oncology trials. The instrument's 30 items are divided among five functional scales (physical, role, cognitive, emotional, and social), nine symptom scales (fatigue, pain, nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), and a global health/quality of life scale. Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher values indicate better functioning or quality of life or a higher level of symptoms. A clinically meaningful change in score may be regarded as 10 points for the various scales of the EORTC QLQ-C30.[30]

The EORTC QLQ-H&N35 is a validated measure of concerns and symptoms specific to cancers of the head and neck.[35] The questionnaire's 35 items are divided among multi-item scales measuring pain (four items), swallowing (four items), problems with social eating (four items) or contact (five items), speech problems (three items), sensory problems (two items), and diminished sexual interest/ fulfilment (two items); single-item measures of problems with the teeth, opening of the mouth, dry mouth, sticky saliva, coughing, feeling unwell, and weight loss or gain; and single item measures of painkiller, nutritional supplement, and feeding tube use.

The EQ-5D-3L[36] is a generic multi-attribute health-state classification system by which health is described in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using three levels: no problems, some problems, and severe problems. Responses to these five dimensions are converted into one of 243 unique EQ-5D health state descriptions, which range between no problems on all five dimensions (11111 i.e. score 1 on each dimension) to severe/extreme problems on all five dimensions (33333). Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility representing the societal desirability of his/her own health. In addition, the EQ-5D includes a visual analogue scale (VAS) allowing a respondent to rate his/her health on a scale ranging from 0-100 with 0 being the worst health state imaginable and 100 being the best health state imaginable. A clinically meaningful change in EQ-5D-3L VAS score may be regarded as seven points.[31] EQ-5D outcomes have been used in the economic model.

Completion rates, calculated as a percentage of patients on study, ranged from 71% to 81% at baseline for all three instruments. After 45 weeks of follow-up, fewer than 10 patients were eligible for on-study assessment of patient-reported health related quality of life (HRQoL) outcomes.[25] Results at baseline and at two follow-up points, which were defined in the CSR, are reported in Table 4.7 (Table S.10.7 in the CSR) for the Global Health Status scale of the EORTC-QLQ-C30, the Pain scale of the EORTC QLQ-H&N35 and the VAS of the EQ-5D.[25] As can be seen from these data, differences between groups were minimal at first follow-up and numbers of patient included at second follow-up are very small. The utility values obtained from the EQ-5D-3L were presented in Section 5.4.1 of the CS as part of the economic analysis of nivolumab versus comparators and discussed in Section 5.2.8 of the ERG report.

Table 4.7: Overview of results on quality of life from CheckMate 141

	Nivolumab 3mg/kg (N=240)		Investigator's Choice (N=121)	
	N	**Mean (SD)**	**N**	**Mean (SD)**
EORTC QLQ-C30 – Global health status[a]				
Baseline	188	55.0 (23.64)	91	57.4 (21.21)
FOLLOW-UP 1* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP 2* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-H&N35 – Pain[b]				
Baseline	193	27.8 (27.84)	91	26.2 (27.43)
FOLLOW-UP 1* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP 2* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D – VAS[c]				
Baseline	185	51.2 (27.34)	87	57.9 (29.42)
FOLLOW-UP 1* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP 2* Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]

Source: CheckMate 141 CSR (7th June 2016)[25] [a] Table S.10.7; [b] Table S.10.9; [c] S.10.10

Notes: * All questionnaires completed at baseline and on-study have been assigned a time-point. In case a patient has two on-study assessments within the same window, the assessment closest to the time-point was used. And in the case of two assessments at a similar distance to the time-point, the latest one was chosen. In the event where the patient had no assessment at all in a specific window, the observation was treated as missing for that time-point. Follow-up 1 = Last dose date -to Last dose date + 58 days; Follow-up 2 = Last dose date + 59 days to Last dose date +102 days

CSR = clinical study report; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire; EORTC QLQ-H&N35 = European Organisation for Research and

	Nivolumab 3mg/kg (N=240)		Investigator's Choice (N=121)	
	N	Mean (SD)	N	Mean (SD)
Treatment of Cancer head and neck questionnaire; EQ-5D = European Quality of Life-5 Dimensions; VAS = visual analogue scale				

Adverse effects of treatment

At the time of the clinical database lock (18 December 2015), the majority of patients who received study treatment in CheckMate 141 experienced an AE, regardless of treatment arm.[25] A total of 218 deaths in the all randomised population had occurred at this data cut-off point, with 210 deaths having occurred in the all treated population.[25] In the all treated population, disease progression was the most common cause of death and was responsible for 109/132 (82.5%) deaths in the nivolumab arm and 68/78 (87.2%) deaths in the IC arm.[25] A total of two deaths attributable to study drug toxicity were observed in CheckMate 141; both deaths occurred in the nivolumab arm (Grade 3 pneumonitis and Grade 5 hypocalcaemia).[27]

Nivolumab was generally well tolerated by patients in CheckMate 141 compared to IC of therapy, with a lower proportion of patients receiving nivolumab experiencing Grade 3-4 all-causality AEs, SAEs and discontinuation due to AEs (see Table 4.8).

Table 4.8: Summary of safety analysis in CheckMate 141

Adverse event, n (%)[a, b]	Nivolumab (n=236)		IC (n=111)	
Deaths	132 (55.9)		78 (70.3)	
Deaths due to study drug toxicity	2 (0.8)[c]		0[d]	
	Any grade	Grade 3-4	Any grade	Grade 3-4
All causality AEs	229 (97.0)	97 (41.1)	109 (98.2)	58 (52.3)
Drug-related AEs	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
All-causality SAEs	127 (53.8)	66 (28.0)	66 (59.5)	36 (32.4)
Drug-related SAEs	16 (6.8)	11 (4.7)	17 (15.3)	12 (10.8)
All-causality AEs leading to treatment discontinuation	51 (21.6)	27 (11.4)	27 (24.3)	12 (10.8)
Drug-related AEs leading to treatment discontinuation	9 (3.8)	6 (2.5)	11 (9.9)	7 (6.3)

Source: Based on Table 18 of the CS[1]

Notes: [a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy. b AEs were coded using the MedDRA version 18.1 and were graded for severity according to the NCI CTCAE version 4.0. c Two deaths in the nivolumab arm (Grade 3 pneumonitis and Grade 5 hypocalcaemia) were assessed as related to study drug. d In the IC arm, there was 1 death in a patient with a Grade 5 drug-related AE (lung infection) that was not attributed to study drug toxicity; Database lock of 18th December 2015.

AEs = adverse events; IC = investigator's choice; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAEs = serious adverse events.

AEs of any cause that occurred in at least 10% of patients in either treatment arm are presented in Table 4.9.

The most frequently reported AEs of any cause in the nivolumab arm were fatigue (26.3%), nausea (19.1%), anaemia (18.6%), decreased appetite (18.6%), malignant neoplasm progression (18.2%), and constipation (15.3%) for any grade; and anaemia (5.9%), dyspnoea (5.5%), hyponatremia (4.7%), dysphagia (3.8%), and pneumonia (3.8%) for grade 3-4.[25]

In the IC arm, the most frequently reported AEs of any cause were anaemia (33.3%), fatigue (32.4%), nausea (30.6%), diarrhoea (23.4%), malignant neoplasm progression (22.5%), and asthenia (21.6%) for any grade; and anaemia (8.1%), hyponatremia (8.1%), neutropenia (7.2%), fatigue (6.3%), and pleural effusion (4.5%) for grade 3-4.[25]

Table 4.9: All-cause AEs in ≥10% patients in either treatment arm in CheckMate 141

Adverse event, n (%)[a, b]	Nivolumab (n=236)		IC (n=111)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Total patients with an event	229 (97.0)	97 (41.1)	109 (98.2)	58 (52.3)
General disorders and administration site conditions	134 (56.8)	17 (7.2)	79 (71.2)	16 (14.4)
Fatigue	62 (26.3)	8 (3.4)	36 (32.4)	7 (6.3)
Pyrexia	30 (12.7)	1 (0.4)	16 (14.4)	3 (2.7)
Asthenia	24 (10.2)	5 (2.1)	24 (21.6)	4 (3.6)
Mucosal inflammation	8 (3.4)	0	17 (15.3)	2 (1.8)
Gastrointestinal disorders	129 (54.7)	19 (8.1)	73 (65.8)	11 (9.9)
Nausea	45 (19.1)	1 (0.4)	34 (30.6)	1 (0.9)
Constipation	36 (15.3)	2 (0.8)	20 (18.0)	0
Diarrhoea	35 (14.8)	2 (0.8)	26 (23.4)	3 (2.7)
Dysphagia	29 (12.3)	9 (3.8)	15 (13.5)	3 (2.7)
Vomiting	27 (11.4)	1 (0.4)	14 (12.6)	0
Respiratory, thoracic and mediastinal disorders	107 (45.3)	38 (16.1)	47 (42.3)	12 (10.8)
Cough	32 (13.6)	1 (0.4)	10 (9.0)	0
Dyspnoea	32 (13.6)	13 (5.5)	12 (10.8)	2 (1.8)
Metabolism and nutrition disorders	106 (44.9)	34 (14.4)	56 (50.5)	21 (18.9)
Decreased appetite	44 (18.6)	3 (1.3)	22 (19.8)	4 (3.6)
Hyponatraemia	22 (9.3)	11 (4.7)	14 (12.6)	9 (8.1)
Investigations	81 (34.3)	18 (7.6)	33 (29.7)	9 (8.1)
Weight decreased	31 (13.1)	0	16 (14.4)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	64 (27.1)	8 (3.4)	33 (29.7)	2 (1.8)
Malignant neoplasm progression	43 (18.2)	5 (2.1)	25 (22.5)	2 (1.8)
Skin and subcutaneous tissue disorders	62 (26.3)	1 (0.4)	40 (36.0)	8 (7.2)
Dry skin	11 (4.7)	0	12 (10.8)	0
Alopecia	2 (0.8)	0	14 (12.6)	3 (2.7)
Blood and lymphatic system disorders	58 (24.6)	22 (9.3)	44 (39.6)	20 (18.0)
Anaemia	44 (18.6)	14 (5.9)	37 (33.3)	9 (8.1)

Source: Tables 19 and 20 of the CS[1]

Notes: [a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy. b AEs were coded using the MedDRA version 18.1 and were graded for severity according to the NCI CTCAE version 4.0; Database lock of 18th December 2015.

AE = adverse event; CS = company submission; IC = investigator's choice; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

'Select' AEs, defined as AEs with a potential immunological cause that are of special clinical interest with the use of nivolumab, were analysed according to organ category (skin, gastrointestinal, endocrine, pulmonary, hepatic, and renal). The most frequently reported any-grade drug-related 'select' AE categories in the nivolumab arm were skin (15.7%), endocrine (7.6%) and gastrointestinal (6.8%).[27] A summary of drug-related 'select' AEs reported in CheckMate 141 is presented in Table 4.10.

Table 4.10: Drug-related 'select' AEs in CheckMate 141

'Select' adverse event, n (%)[a]	Nivolumab (n=236)		IC (n=111)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Total patients with an event, by category				
Skin	37 (15.7)	0	14 (12.6)	2 (1.8)
Endocrine	18 (7.6)	1 (0.4)	1 (0.9)	0
Gastrointestinal	16 (6.8)	0	16 (14.4)	2 (1.8)
Hepatic	5 (2.1)	2 (0.8)	4 (3.6)	1 (0.9)
Pulmonary	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/infusion reactions	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal	1 (0.4)	0	2 (1.8)	1 (0.9)
Drug-related 'select' AEs, by category				
Skin				
Rash	18 (7.6)	0	5 (4.5)	1 (0.9)
Pruritus	17 (7.2)	0	0	0
Rash maculo-papular	5 (2.1)	0	1 (0.9)	0
Eczema	2 (0.8)	0	0	0
Skin exfoliation	2 (0.8)	0	0	0
Erythema	1 (0.4)	0	4 (3.6)	1 (0.9)
Exfoliative rash	1 (0.4)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	1 (0.4)	0	2 (1.8)	1 (0.9)
Rash macular	1 (0.4)	0	1 (0.9)	0
Urticaria	1 (0.4)	0	0	0
Dermatitis	0	0	2 (1.8)	0
Endocrine				
Thyroid disorder				
Hypothyroidism	9 (3.8)	0	1 (0.9)	0
Blood thyroid stimulating hormone increase	3 (1.3)	0	0	0
Hyperthyroidism	2 (0.8)	0	0	0
Thyroid function test abnormal	2 (0.8)	0	0	0
Thyroiditis	2 (0.8)	0	0	0
Pituitary disorder				
Hypophysitis	1 (0.4)	1 (0.4)	0	0
Hypopituitarism	1 (0.4)	0	0	0

'Select' adverse event, n (%)[a]	Nivolumab (n=236)		IC (n=111)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Adrenal disorder				
Secondary adrenocortical insufficiency	1 (0.4)	1 (0.4)	0	0
Gastrointestinal				
Diarrhoea	16 (6.8)	0	15 (13.5)	2 (1.8)
Colitis	0	0	1 (0.9)	0
Hepatic				
Alanine aminotransferase increased	2 (0.8)	1 (0.4)	3 (2.7)	1 (0.9)
Aspartate aminotransferase increased	2 (0.8)	0	2 (1.8)	0
Blood alkaline phosphatase increased	2 (0.8)	0	0	0
Transaminases increased	2 (0.8)	1 (0.4)	0	0
Blood bilirubin increased	1 (0.4)	0	0	0
Liver function test abnormal	1 (0.4)	1 (0.4)	0	0
Gamma-glutamyltransferase increased	0	0	1 (0.9)	1 (0.9)
Hepatic enzyme increased	0	0	1 (0.9)	0
Pulmonary				
Pneumonitis	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/infusion reactions				
Infusion-related reaction	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal				
Acute kidney injury	1 (0.4)	0	2 (1.8)	1 (0.9)

Source: Table 21 of the CS[1]

Notes: [a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy; 'Select' AEs were identified based on the following guiding principles: 1) AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies; 2) AEs that may require immunosuppression (e.g. corticosteroids) as part of their management; 3) AEs whose early recognition and management may mitigate severe toxicity; and 4) AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterisation; Database lock of 18th December 2015.

AEs = adverse events; CS = company submission; IC = investigator's choice.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

This is strictly not relevant given that there was no meta-analysis.**ERG comment:** The ERG did request a review of the paclitaxel trials that were identified in Table 17 of the CS.[1] Although no indirect comparison is possible, the ERG believed it to be useful to see the results of these studies in order to help to validate the claim that there are no differences between paclitaxel and any of the therapies in the Investigator Choice arm of the CheckMate 141 trial. The company responded by including three tables (6 to 8), which are reproduced below as Tables 4.11 to 4.13.[11] These data are useful to validate the separate claim that there is no difference between paclitaxel and docetaxel, as mentioned in the clarification letter Question B3.[10] The company response (page 63) continued to claim this to be the case and re-cited the same basis i.e. *"In the absence of any definitive clinical data, an assumption of equivalence between docetaxel and paclitaxel, in terms of OS specifically, was presented in the CS, based on clinician feedback"*.[11]

Table 4.11: Summary of methodology of five paclitaxel studies

Trial	Trial design	Population	Intervention	Comparator(s)	Primary study reference; *Secondary study reference(s)*
BERIL-1	Phase II, randomised study	Patients with platinum pre-treated R/M SCCHN	Paclitaxel (i.v. 80 mg/m^2 weekly) plus placebo; n=79	Paclitaxel (i.v. 80 mg/m^2 weekly) plus buparlisib (oral 100mg daily); n=79	Soulieres 2016[37], Licitra 2016[38]
Tahara 2011	Phase II, single-arm study	Patients with R/M SCCHN and one or no prior chemotherapy regimens	Paclitaxel (i.v. 100 mg/m^2 once weekly for 6 weeks of a 7-week cycle); n=74	N/A	Tahara 2011[39]
Caballero 2007	Before-and-after study	Patients with R/M SCCHN refractory to platinum-based therapies	Paclitaxel (i.v. 80 mg/m^2 once weekly for 6 weeks); n=33	N/A	Caballero 2007[40]
Grau 2009a	Phase II, single-arm study	Patients with platinum-resistant R/M SCCHN	Paclitaxel (i.v. 80 mg/m^2 once weekly for 6 weeks); n=60	N/A	Grau 2009a[41]
Grau 2009b	Single-arm study	Patients with SCCHN and progression following platinum-based chemotherapy	Paclitaxel (i.v. 80 mg/m^2 once weekly for 6 weeks); n=47	N/A	Grau 2009b[42]

Source: Based on Table 6 of the response to the request for clarification[11]
N/A = not applicable; R/M = relapsed or metastatic; SCCHN = Squamous cell carcinoma of the head and neck

Table 4.12: Summary of baseline characteristics across the five paclitaxel studies

	Tahara 2011	BERIL-1 (BUP + PAC)	BERIL-1 (PAC + PBO)	Caballero 2007	Grau 2009a	Grau 2009b
Gender (n [%])						
Male	56 (77.8)	NR	NR	30 (91)	55 (91.7)	4 (8.5)
Female	16 (22.2)	NR	NR	3 (9)	5 (8.3)	43 (92.5)
Age (median ([range])	61 (41–74)	59 (NR)	58 (NR)	58 (46–80)	59.5 (45–79)	57 (46–80)
ECOG PS (n [%])						
0	48 (66.7)	NR	NR	0 (0)	1 (1.7)	1 (2.1)
1	22 (30.6)	NR	NR	29 (88)	50 (83.3)	37 (78.7)
2	2 (2.8)	NR	NR	4 (12)	9 (15.0)	9 (19.1)
Disease status (n [%])						
Advanced (metastatic)	25 (34.7)	NR	NR	12 (36)	13 (21.7)	16 (34.0)
Recurrent	47 (65.3)	NR	NR	14 (43)	31 (51.7)	27 (57.4)
Both	NR	NR	NR	7 (21)	16 (26.4)	4 (8.5)
Primary location (n [%])						
Oral cavity	8 (11.1)	NR	NR	10 (30)	NR	12 (25.5)
Paranasal cavity	8 (11.1)	NR	NR	NR	NR	NR
Nasopharynx	8 (11.1)	NR	NR	NR	NR	NR
Oropharynx	12 (16.7)	NR	NR	12 (37)	30 (50)	12 (25.5)
Hypopharynx	18 (25.0)	NR (29)	NR (39)	NR	10 (16.7)	7 (14.9)
Larynx	6 (8.3)			NR	20 (33.3)	NR
Salivary gland	7 (9.7)	NR	NR	NR	NR	NR
Supraglottis	NR	NR	NR	6 (18)	NR	10 (21.3)
Glottis	NR	NR	NR	5 (15)	NR	6 (12.8)

	Tahara 2011	BERIL-1 (BUP + PAC)	BERIL-1 (PAC + PBO)	Caballero 2007	Grau 2009a	Grau 2009b
Prior treatment						
Chemotherapy[a]	62 (86.1)	NR	NR	NR	32 (53.3)[b]	47 (100)
Platinum-based chemotherapy	55 (76.4)	NR	NR	NR		
Surgery	36 (50.0)	NR	NR	NR	38 (62.3)	
Radiotherapy	60 (83.3)	NR	NR	NR	15 (24.6)	
Chemotherapy plus radiotherapy	NR	NR	NR	NR	7 (11.5)	
Other	7 (9.7)	NR	NR	NR	NR	

Source: Based on Table 7 of the response to the request for clarification[11]
Notes: [a] Including adjuvant chemotherapy, neoadjuvant chemotherapy, and chemoradiotherapy; [b] Previous palliative chemotherapy
BUP = buparlisib; ECOG = Eastern Cooperative Oncology Group; NR = not reported; PAC = paclitaxel; PBO = placebo; PS = performance status

Table 4.13: Summary of outcomes across the five paclitaxel studies

	Tahara 2011	BERIL-1 (BUP + PAC)	BERIL-1 (PAC + PBO)	Cabellero 2007	Grau 2009a	Grau 2009b
ORR (CR +PR + stable disease)	30.4%	39%	14%	61%	58.3%	NR
Median PFS (95% CI)	3.2 months (2.5–6.7)	4.6 months (NR)	3.5 months (NR)	NR	6.2 months (3.7 – 8.6) (responding patients)	5.1 months (NR) (responding patients)
Median OS (95% CI)	11.4 months (7.4–19.4)	10.0 months (NR)	6.5 months (NR)	NR	8.5 months (5.7–11.2) (responding patients) 3.4 months (2.0–4.9) (non-responding patients)	5.6 months (NR)

Source: Based on Table 8 of the response to the request for clarification[11]
BUP = buparlisib; CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; NR = not reported; ORR = objective response rate; PAC = paclitaxel; PBO = placebo; PFS = progression-free survival; PR = partial response; PS = performance status

As shown in Table 4.11, each of these studies is a trial of the treatment of interest i.e. paclitaxel and, in all but one study (Tahara 2011[39]), at the dose used in the economic analysis, i.e. 80 mg/m^2 once weekly. The population does vary between the studies, but the same four out of five studies might reasonable be considered to be in the population of interest to this appraisal, i.e. R/M SCCHN with prior platinum-based therapy.[7]

The baseline characteristics are shown in Table 4.12. Unfortunately, the studies vary in the completeness of reporting. Of the four most comparable studies, one reports virtually no characteristics.[37, 38] The other three do report probably sufficient characteristics to compare with the CheckMate 141 trial.[40-42]

Age seems comparable in all studies. In terms of gender, two studies, Caballero 2007 and Grau 2009a, are roughly comparable with the majority being male.[40, 41] Grau 2009b appears to be quite different with the majority being female.[42] The distribution of the site of the primary tumour is different to CheckMate 141, although the effect of this is difficult to predict. The most important reported difference is probably in terms of Eastern Cooperative Oncology Group performance status (ECOG PS). Although across all studies the majority of patients have a value of 1, in two studies, Caballero 2007 and Grau 2009a, a substantial minority have a value of 2, in contrast to the CheckMate 141 trial, where only four patients had this value.[40, 41] The importance of this is that it might mean that outcomes and OS in particular would be likely to be worse in the paclitaxel studies, at least those by Caballero 2007 and Grau 2009a.

Interestingly, despite the prediction that, according to ECOG PS, outcomes would be most likely to be worse in Caballero 2007 and Grau 2009a, they appear to be better than in the CheckMate 141 trial.[1, 40, 41] In particular, median OS was 8.5 months in Grau 2009a versus 7.5 months for nivolumab, 5.1 months for IC and [redacted] months for docetaxel.[41] Indeed, only in Grau 2009b, which is the population of mainly women, was the median OS close to that in the docetaxel group.[42] Unfortunately, OS was not reported in Cabellero 2007 and neither was PFS, although it was also longer in the other paclitaxel studies than in either nivolumab, IC or the docetaxel group. As shown in Table 4.13, ORR was much higher for paclitaxel in any study than IC, where it was only 7%, as reported in Table 16 in the CS.[1] It was also higher in both Cabellero 2007 and Grau 2009a than for nivolumab, although it was lower in the paclitaxel arm of BERIL-1.[37, 38, 40, 41]

In conclusion, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

This is not relevant given that there was no meta-analysis.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG included a detailed discussion of the paclitaxel trials that were identified in the CS (see Section 4.3).

4.6 Conclusions of the clinical effectiveness section

Based on the company response[11] to a clarification question[10] regarding the representativeness of the CheckMate141 trial, the company seems to believe that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy. The ERG considers this to be reasonable.

The company did seem to include all relevant controlled trials given that the inclusion criteria were broad enough not to exclude on the basis of design or any of the comparators.[1] However, it appears that there is only one RCT that at least approximately matches the population in the scope i.e. CheckMate 141. Unfortunately, it lacks any comparison with one of the comparators i.e. paclitaxel. Also, it does have some significant limitations, including a comparison not with the comparators in the scope, but with IC, which permits clinician choice of treatment. This therefore means that the ITT analysis prevents an unbiased estimate of the effectiveness of nivolumab versus any of the comparators. It did, however, show a statistically significant advantage in OS versus IC, which might be considered an unbiased estimate versus standard care, but only if IC was made on the same basis as that in clinical practice. However, there is no way of knowing that and it would have to mean that precisely the same proportion of patients was eligible for each of the therapies (methotrexate, docetaxel and cetuximab) as in the trial. To compound the problem, one of the choices was cetuximab, which is not in the scope.[7] Therefore, the ERG considers that the representativeness of the CheckMate 141 trial to UK clinical practice is highly questionable most particularly in terms of patient characteristics that would determine both intended treatment and prognosis.

The ERG did ask in the clarification letter for analyses to attempt to overcome these two main limitations: inclusion of cetuximab and no comparison with paclitaxel.[10] In response, the company did demonstrate little effect of the removal of the cetuximab patients, which was likely given the small number (n=15).[11] They also provided three tables which summarised the design, baseline characteristics and outcomes of five paclitaxel trials. The ERG concluded that, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab. Also, the response to a clarification question regarding the difference in the HR for OS between the EU and North America highlighted the difference in percentage receiving each of the treatments in the scope (docetaxel and methotrexate). [11] The ERG would therefore conclude that, whilst it is reasonable to believe that nivolumab extends life expectancy, it is impossible to be confident by how much in comparison to any treatment in the scope or which is considered to be standard care in the UK.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Searches for cost effectiveness analysis review

A literature review was conducted to identify evidence to inform development of a model for nivolumab to treat platinum-refractory recurrent or metastatic SCCHN. A single search and review was conducted to identify relevant SCCHN studies including: economic evaluations, studies reporting cost/resource use data and also those reporting utility values. Searches were reported for Embase, MEDLINE, MEDLINE In-Process, the Health Technology Assessment Database (HTA) and the NHS Economic Evaluation Database (NHS EED). The host provider for each database was listed and the date the searching was conducted was provided.

Searches were limited from 2005 to 2015. The Embase and MEDLINE search was conducted via the Embase.com platform, and was limited to English language publications only. A PubMed search was carried out to identify e-Pubs and recent references not yet added to MEDLINE, and no language limit was applied to this search.

ERG comment: The ERG noted that searches of conference proceedings were carried out, from 2013-2015 (where available). These searches covered six different conference proceedings, including: American Society of Clinical Oncology (ASCO), ASCO Quality Care Symposium (ASCO-QoC), Academy of Managed Care Pharmacy (AMCP), European Society for Medical Oncology (ESMO), American Head and Neck Society (AHNS) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Search strategies for the database searches were provided in Appendix 6 of the CS [13] and were well reported. The ERG was not able to reproduce the Embase.com search, due to lack of access to that host.

These meet the requirements detailed in the NICE guide to the methods of technology appraisal.[16]

For the most part, the database searches were clearly structured and used combinations of index terms appropriate to the resource searched, free text and a number of synonyms for the condition, intervention and most of the comparators. It was not clear whether a validated study design filter was used for the cost effectiveness facet of search terms.

As with the original clinical effectiveness searches (Section 4.1.1), MEDLINE and Embase were searched simultaneously via the Embase.com interface using the synonym function. The same limitations regarding reliance on in-built synonym matching and automatic mapping to equivalent MeSH indexing applied, which may have resulted in a less sensitive search. The ERG was not able to investigate the implications of this approach due to lack of access to the Embase.com interface.

Due to the Embase.com searches being limited to English language results only, the same limitations discussed earlier in the clinical effectiveness section apply. The ERG was concerned about the language

bias of restricting the searches to English language only; this is not in line with current best practice.[17, 18, 20-23]

The PubMed and Cochrane Library searches did not incorporate an English language limit, and following clarification, the company reported this restriction had been applied during screening.[11]

The company's economics searches were a year older than those included in the clinical effectiveness sections, however a partial update of Embase.com and PubMed was undertaken and screened in response to the clarification letter.[11] The company reported conducting an update search for Embase, PubMed and three conference proceedings, with the total number of records retrieved. The strategy and database host used was not reported, and the date of the update search was not provided.

The ERG considered the concurrent MEDLINE and Embase searches to be satisfactory in structure in addressing retrieval of economic evaluations and cost studies, however the English language limit may have introduced a language bias.

Measurement and valuation of health effects

The cost effectiveness searches reported in Section 5.1 and Appendix 6 of the CS were used to inform this section.[1]

ERG comment: The study design filters were not referenced and did not appear to be published objectively derived filters. The filters contained a combination of subject heading terms and free text terms to capture literature referring to costs, economics or utilisation, however no additional terminology to health-related quality of life (HRQoL) studies were included. The search would have greatly benefited from inclusion of additional indexing and free-text terms to identify quality of life, HRQoL and specific instruments, such as the EQ-5D or SF-36. The ERG therefore believes that although relevant data from the CheckMate 141 trial were included in the model, this approach does not meet with NICE requirements.[43] The ERG did not consider this approach appropriate, furthermore the same limitations concerning the simultaneous Embase.com search and the English language restriction also apply here.

Cost and healthcare resource identification, measurement and valuation

The cost effectiveness searches reported in Section 5.1 and Appendix 6 of the CS were used to inform this section.[1]

ERG comment: The study design filters were not referenced and did not appear to be published objectively derived filters. The filters contained a combination of subject heading terms and free text terms to capture literature referring to costs, economics or utilisation. The ERG considered this approach adequate, although the same limitations concerning the simultaneous Embase.com search and the English language restriction also apply here.

5.1.2 Inclusion/exclusion criteria used in the cost effectiveness review

Screening of publications by title and abstract was performed; followed by full publication review. Eligibility criteria for the review are presented in Table 5.1.

Table 5.1: Eligibility criteria for the economic systematic literature review

Eligibility domain	Inclusion criteria	Exclusion criteria
Population	Adult patients with stage III/IV SCCHN	-
Intervention(s)	• Nivolumab • Docetaxel • Methotrexate • Paclitaxel And other approved/ investigational agents: cetuximab; fluorouracil; bleomycin; cisplatin; cetuximab; temoporfin; cabazitaxel; irinotecan; afatinib; zalutumumab; gefitinib; carboplatin; lapatinib; bevacizumab; panitumumab; nimotuzumab; capecitabine; erlotinib; canertinib; mpdl3280a; sorafenib; axitinib; buparlisib; mk-1775; pembrolizumab; medi4736; oxaliplatin; epirubicin; gemcitabine; vinorelbine; ifosfamide; pemetrexed; advexin; regorafenib	-
Comparator(s)[a]	• Any active pharmacological agent • Therapy of investigator's choice • Placebo • Best supportive care	-
Outcomes(s)	• Economic outcomes such as cost effectiveness and/or cost utility including ICER/ICUR, cost/QALY, cost/LYG, cost/DALY, sensitivity analyses results • Direct/indirect costs, resource use data reported in economic evaluations • QALY, DALY, LYG • Utility/disutility data associated with disease and adverse events including EQ-5D, time trade off, standard gamble, etc.	-
Study design 1 (Published economic evaluations)	• Cost effectiveness analyses • Cost utility analyses • Cost benefit analyses • Cost minimisation analyses • Budget impact models • Cost consequence studies • All economic evaluation studies based on models	• Case studies • Case series • Case reports
Study design 2 (Cost/resource use studies)	• Cost studies/surveys/analyses • Database studies collecting cost data (e.g. claims databases and hospital records) • Resource surveys	
Study design 3 (Utility studies)	• Studies reporting utility data[b]	

Eligibility domain	Inclusion criteria	Exclusion criteria
Other considerations	• Full-text articles published in English language • Published 2005–2015	Full-text articles in any other language to English

Source: Based on Table 23 of the CS[1]
Notes: [a] Only applicable to published economic evaluations; [b] Studies exclusively reporting HRQoL data were not included in this review
CS = company submission; DALY = Disability Adjusted Life Years; EQ-5D = EuroQol-5D; HRQoL = health-related quality of life; ICER = Incremental Cost effectiveness Ratio; ICUR = Incremental Cost Utility ratio; QALY = Quality Adjusted Life Years

ERG comment: The English language limit restricted the sensitivity of the search and may have introduced a language bias. The remaining in- and exclusion criteria seem appropriate for the objective of this review.

5.1.3 Included/excluded studies in the cost effectiveness review

The search resulted in 3,469 unique articles after removal of duplicates. After screening, 44 articles (representing 43 unique studies) were included in the review. Four of these studies were economic evaluations (Table 5.2). None of the included studies were performed from the UK National Health Service (NHS)/Personal Social Services (PSS) perspective and none evaluated the cost effectiveness of nivolumab or concerned R/M SCCHN patients who progressed after platinum-based therapy.

Relevant studies concerning health-related quality of life evidence and resource use and costs are briefly described in Sections 5.2.8 and 5.2.9, respectively. Appendix 7 of the CS provides an overview of studies excluded during full-text screening and Appendix 9 of the CS presents the quality assessment of the included studies.[13]

ERG comment: The ERG agrees that none of the identified studies was performed from the UK NHS/PSS perspective and concerned the population or intervention of interest.

Table 5.2: Summary of published economic evaluations included in the economic systematic literature review

Study (Year)	Country and perspective	Summary of the model	Patient population	QALYs	Costs (currency)	ICER (per QALY gained)
Greskovich 2014[44] (abstract only)	Not reported; payer perspective (direct costs)	Revenue and cost data were collected from patients randomly assigned to chemoradiation with either outpatient cisplatin or inpatient cisplatin plus 5-fluorouracial	Stage III/IVB non-nasopharynx SCHHN treated with chemoradiation Intervention: radiotherapy plus outpatient cisplatin Comparator: radiotherapy plus inpatient cisplatin plus 5-fluorouracial	Not reported	Incremental costs = $18,664	Not reported
Hannouf 2012[45]	Canada; public perspective (direct and indirect costs)	Markov state transition model: Patients entered one of two models based on choice of therapy ("P" = platinum-based chemotherapy or "C" = cetuximab plus platinum-based chemotherapy). Health states included stable disease, progressed disease and death. Additional health states were present in model "C" to account for cetuximab-specific AEs. Transitions between health states were based on clinical data from the EXTREME trial. Cycle length = 1 month Time horizon = 3 years	First-line treatment of R/M SCCHN Intervention: cetuximab plus platinum-based chemotherapy Comparator: platinum-based chemotherapy alone	Incremental: 0.093	Incremental: $36,000	$386,000 per QALY

Study (Year)	Country and perspective	Summary of the model	Patient population	QALYs	Costs (currency)	ICER (per QALY gained)
Fountzilas 2006[46]	Greece; National Health Service perspective (direct costs)	Survival, treatment cost per patient and healthcare resource utilisation were collected as part of a randomised trial in which patients were randomly assigned to either paclitaxel and gemcitabine (Group A) or paclitaxel and pegylated liposomal doxorubicin (Group B). The survival analysis showed no difference between treatment arms and so the analysis was based only on treatment costs (cost minimisation).	Locally advanced or R/M non-nasopharyngeal SCCHN treated with chemotherapy Intervention: paclitaxel and gemcitabine Comparator: paclitaxel and pegylated liposomal doxorubicin	Not reported (No difference in survival)	Group A: €7,419 Group B: €11,068 Incremental costs = €-3,649	Not reported
Van Rooijen 2012[47] **(abstract only)**	Not reported	Not reported (Evaluated the effect of combining RCT and real-world data on ICERs)	Locally advanced head and neck cancer Intervention: cetuximab Comparator: placebo	Not reported	Not reported	€5,000 per QALY difference when using unadjusted RCT data

Source: Based on Appendix 8 of the CS[13]

CS = company submission; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; R/M = recurrent or metastatic; RCT = randomised controlled trial; SCCHN = squamous-cell carcinoma of the head and neck

5.1.4 Conclusions of the cost effectiveness review

The CS provides an overview of the included studies but no specific conclusion is formulated.

ERG comment: Since the identified studies were not performed from the perspective of interest or concerned the population or intervention of interest, the ERG agrees that no specific conclusion from the review could be formulated.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.3: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	A partitioned-survival model was constructed to evaluate the cost effectiveness of nivolumab compared with docetaxel, methotrexate and paclitaxel in R/M SCCHN patients who progressed after platinum-based therapy		5.2.2 (p. 95-97)
States and events	The model was based on disease progression, consisting of the health states pre-progression, post-progression and death.	Health states were selected according to the clinical pathway of care and comparable to the structure used in other late-stage cancer models.	5.2.2 (p. 95)
Comparators	• Docetaxel • Methotrexate • Paclitaxel	Taxane-based therapies (docetaxel, paclitaxel) would be administrated in this setting. However, in case of intolerance, methotrexate would be considered as alternative treatment.	5.2.3 (p. 97-98)
Population	Patients with R/M SCCHN who have progressed after platinum-based therapy		5.2.1 (p. 95)
Treatment effectiveness	Nivolumab 3 mg/kg administrated once every two weeks	This is the dose specified in the marketing authorisation	5.2.3 (p.97)
Adverse events	The health related quality of life and health care costs consequences of the following adverse events were incorporated in the first cycle of the cost effectiveness model: Fatigue, Dyspnoea, Hyponatraemia, Anaemia, Neutropenia, Dysphagia, Nausea and vomiting and Anorexia. Only Grade 3/4	Adverse event rates were based on the CheckMate141 trial.	5.3.6 (p. 126-127)

	Approach	Source / Justification	Signpost (location in CS)
	adverse events were taken into account.		
Health related QoL	Health related quality of life data was collected in the CheckMate141 trial. These quality of life data were used for to calculate health state utility values while the impact of adverse events on quality of life was obtained from the literature.	CheckMate 141 and literature.	5.4 (p.127-133)
Resource utilisation and costs	Treatment costs, subsequent therapy costs, health state costs and adverse event costs were taken into account in the economic model. Treatment costs were based on the weight of the European population of CheckMate 141 and on TTD curves according to CheckMate 141. Nivolumab costs equalled [redacted] per dose (or [redacted] per cycle) at list price. The proportions of patients receiving subsequent treatment were treatment-dependent and based on CheckMate 141. Health state costs and adverse event costs were based on literature. The unit costs and frequency of resource use per cycle was assumed to be independent constant between PF and PD health states but the proportion of patient using each resource was different between both health states.	CheckMate 141 for treatment costs. Docetaxel QW ($30mg/m^2$) was considered in the model, which is consistent with CheckMate 141 but inconsistent with UK practices where Docetaxel Q3W ($75mg/m^2$) is more often prescribed. Unit prices for resource use included in the health state costs and adverse event costs were based on NHS references costs. The proportion of patients receiving each resource use item in each health state was based on literature.	5.5 (p. 134- 142)
Discount rates	Discount of 3.5% for utilities and costs	As per NICE scope	5.2.2 (p. 97)
Sub groups	No subgroups were considered		5.9 (p.181)
Sensitivity analysis	Both DSA and PSA were performed as well as diverse scenario analyses. The model was the most sensitive to the choice of utility value for the progressed health state and to the choice of parametric		5.8 (p. 155-181)

	Approach	Source / Justification	Signpost (location in CS)
	distributions for either TTD or OS		

CS = company submission; DSA = deterministic sensitivity analysis; EQ-5D-3L = European Quality of Life-5 Dimensions, 3 Levels; ICER = incremental cost effectiveness ratio; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD= progressed disease; PF = progression-free; PSA = probabilistic sensitivity analysis; Q3W = once every three weeks; QALY = quality-adjusted life year; QW = once weekly; R/M SCCHN = recurrent/metastatic squamous cell carcinoma of the head and neck; TTD = time to treatment discontinuation

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

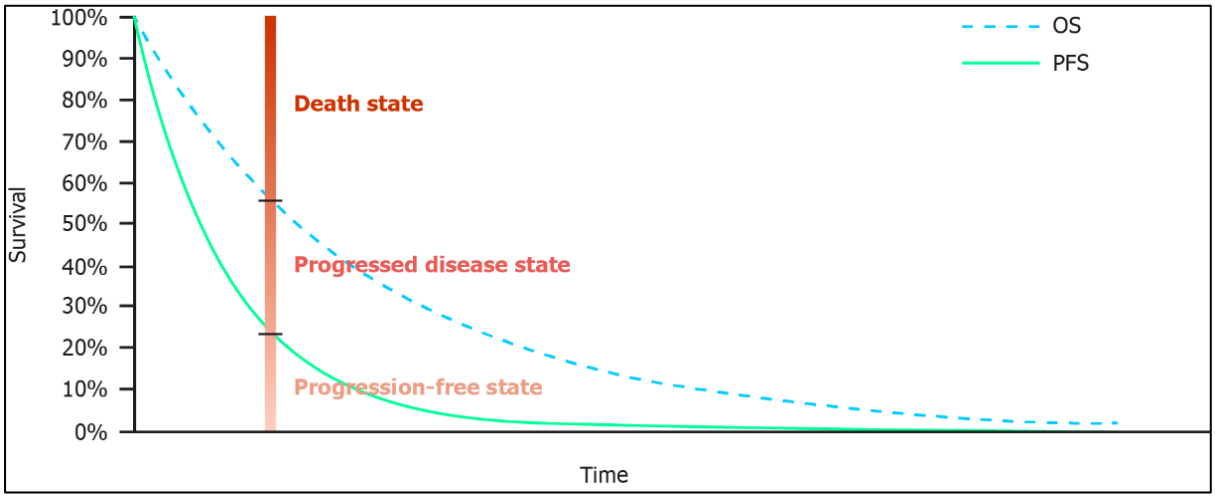
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Yes	As per NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partly	The IC arm is used to inform treatment effectiveness for docetaxel, methotrexate and paclitaxel. However, the IC arm also included treatment with cetuximab that is not licensed in the UK for this indication. Docetaxel dosage, as used in the base-case analysis of the company (and the CheckMate 141 trial), was not the most representative of UK clinical practice.
Type of economic evaluation	Cost effectiveness analysis	Yes	As per NICE reference case
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	As per NICE reference case
Perspective on outcomes	All health effects on individuals	Yes	As per NICE reference case
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	As per NICE reference case. Time horizon is 20 years, which is sufficiently long enough for >99% of patients in the model to have died
Synthesis of evidence in outcomes	Systematic review	Yes	As per NICE reference case. All evidence of effectiveness came primarily from the CheckMate 141 trial.
Measure of health effects	Quality adjusted life years (QALYs)	Yes	As per NICE reference case

Source of data for measurement HRQoL	Described using a standardised and validated instrument	Yes	The EQ-5D-3L health status questionnaire was used to collect HRQoL data for patients in the CheckMate 141 trial.
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Yes	The UK TTO valuations have been used as a default for the EQ-5D-3L questionnaire, converting questionnaire responses to utilities which are applied in the economic model.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	As per NICE reference case
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	As per NICE reference case
Sensitivity analysis	Probabilistic modelling	Yes	As per NICE reference case
EQ-5D-3L = European Quality of Life-5 Dimensions, 3 Levels; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Clinical Excellence; PSA = probabilistic sensitivity analysis; quality-adjusted life years; PSS = Personal Social Services; TTO = Time trade off; UK = United Kingdom			

5.2.2 Model structure

The company developed a cohort-based partitioned survival model consisting of three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. According to the company, the model structure represents the clinical pathway of care of R/M SCCHN treatment and is consistent with previous economic evaluations submitted to NICE in R/M SCCHN (TA172, 2009[48]) and other evaluations of nivolumab appraised by NICE (ID811[49], ID900[50]). Patients enter the model in the PF health state. At the end of each cycle, a patient might remain in the PF health state or enter either the PD or death states. Disease progression was defined by RECIST version 1.1, which was also used in the CheckMate 141 trial. Patients in the PD state can remain in that state or enter the death state, which is an absorbing state. The PFS curve determines the proportion of patients occupying the PF state, as it represents the proportion of patients which are alive and progression-free, while the OS curve is used to determine the proportion of patients occupying the death state, as it represents the proportion of patients who have died. The proportion of patients occupying the PD state was calculated by subtracting the proportion of patients alive and progression-free (based on the PFS curve) from the proportion of patients alive (based on the OS curve). Treatment continuation after progression was allowed in both treatment arms. The model structure is presented in Figure 5.1.

Figure 5.1: Schematic representation of the partitioned survival method



Source: Based on Figure 21 of the CS[1]

Costs and health-related utilities associated with each health state were calculated per cycle. Costs and disutilities associated with AEs were estimated per episode and applied only once, at the beginning of the first cycle, based on the proportion of patients in each treatment arm experiencing each AE. A four week cycle length was used. The model was programmed in Excel.

ERG comment: The model structure is similar to other oncology assessments and seems appropriate for the current decision problem. The model structure is also similar to previous nivolumab appraisals.[49, 50] AEs were incorporated only once in the first cycle. This simplification might underestimate the long-term influence of AEs on the cost effectiveness outcomes. This simplification is expected to have a minor effect on the cost effectiveness results given the relatively small differences between treatments in rate of adverse events.

5.2.3 Population

The economic evaluation considers patients with R/M SCCHN who have progressed after platinum-based therapy. The company states this is consistent with the study population of CheckMate 141, and the anticipated indication for nivolumab in SCCHN and the population outlined in the final scope issued by NICE for this appraisal.

ERG comment: The population represented in the cost effectiveness model seems to correspond to the expected licensed indication and the final scope issued by NICE for the current decision problem.

5.2.4 Interventions and comparators

Nivolumab has been considered within the economic evaluation as per the anticipated licensed indication in SCCHN. Nivolumab was modelled with a posology of 3 mg/kg as a 60-minute infusion. The licence also specifies that nivolumab treatment should be continued until clinical benefit is no longer observed. This aspect of anticipated use with nivolumab is reflected through the use of the time to treatment discontinuation (TTD) curve to model time on treatment instead of the PF curve.

The comparators in the cost effectiveness model are docetaxel, paclitaxel and methotrexate. According to the company, treatment in the platinum-refractory setting would most likely be with a taxane (docetaxel or paclitaxel), or methotrexate if a taxane was clinically inappropriate due to tolerability issues or prior taxane therapy.[51] Single-agent docetaxel is predominantly used in UK clinical practice however paclitaxel may also be used for patients who are not fit enough to receive treatment with docetaxel and have not received prior taxane therapy.[9, 52] In the cost effectiveness model, docetaxel is

assumed to be administrated once weekly at a dose of 30 mg/m^2 while in the UK docetaxel is mostly administrated at a dose of 75mg/m^2 every three weeks, according to the company.[1]

In the IC comparator arm of the CheckMate 141 trial, the majority of patients received docetaxel or methotrexate (47% and 41% respectively), whilst the remaining patients received cetuximab.[26, 27] The company based OS, PFS, TTD, and incidence of AEs for docetaxel and methotrexate in the model on the total IC arm of the CheckMate 141 trial, assuming clinical equivalence between these therapies. The company states this assumption was confirmed by expert clinician feedback and by data from a phase II clinical trial.[5, 53] Furthermore, clinical equivalence was assumed between docetaxel (as observed in the IC arm of the CheckMate 141 trial) and paclitaxel. The company states that this assumption is supported by UK clinical opinion,[5, 9, 52] and necessary because of limited RCT evidence (Section 4.3) for paclitaxel as a monotherapy for the treatment of platinum refractory R/M SCCHN.

ERG comment: The ERG will successively address the following issues: the dosing of nivolumab, the administration schedule and dosing of docetaxel and the equivalence assumptions between docetaxel and paclitaxel and between docetaxel and methotrexate.

The dosing schedule of nivolumab has recently been modified by the US Food and Drug Administration (FDA) from the 3 mg/kg every two weeks to a 240 mg (fixed) dose every two weeks for the treatment of renal cell carcinoma, metastatic melanoma and non-small cell lung cancer.[54] The FDA does not expect this new dose regimen to have efficacy or safety consequences. If the same administration scheme modification takes place in Europe and is also considered relevant for R/M SCCHN, this might increase the acquisition costs (and consequently the cost effectiveness outcomes) of nivolumab since the mean weight of patients in the current assessment is [redacted] and that a 240 mg dose corresponds to a mean weight of 80 kg. The influence of this assumption will be explored in a scenario analysis (see Section 5.3)

The administration schedule of docetaxel applied in the model is not representative of UK daily practice. Therefore, the ERG will use the once every three week administration schedule of docetaxel (75 mg/m^2 per administration) instead of the once weekly administration schedule (30 mg/m^2 per administration) in its base-case analysis because this schedule is more routinely used in the UK and because there is no evidence to support a difference in efficacy between the two docetaxel schemes (response to Clarification Question A8).[11]

In the CS, clinical equivalence between docetaxel and paclitaxel was not supported by clinical evidence. The ERG consequently requested clarification on the justification of this assumption. The company explained that the sources used represent the opinion of two UK clinicians and from an international advisory board.[9, 51, 52] The two UK clinicians emphasised the lack of evidence demonstrating a difference in effectiveness between docetaxel and paclitaxel. However, there is no empirical evidence which supports this assumption. Consequently, uncertainty remains concerning this assumption. The ERG will however maintain this assumption in its base-case since there is no clinical evidence contradicting this assumption or to inform plausible alternative scenario analyses. Moreover, the performance of a systematic search plus network meta-analysis was not feasible for the ERG within the timelines. However, as concluded in Section 4.3, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab. Therefore, a threshold analysis (conditional upon the ERG base-case) will be performed to determine what the relative effectiveness of paclitaxel should be compared to docetaxel in order for paclitaxel to become cost effective compared with nivolumab (Section 5.3.2).

The company assumes equivalence in effectiveness between methotrexate and docetaxel and argues that Guardiola 2004[53] supports this assumption. Even though Guardiola 2004[53] implies that survival curves for methotrexate and docetaxel are 'super-imposable', the study still demonstrates a statistically significant difference in response between methotrexate and docetaxel. In addition, this is a phase II study with 20 and 37 patients randomised to methotrexate and docetaxel respectively. The assumption of equivalence between these treatments is therefore uncertain to the ERG, also considering that methotrexate and docetaxel provide different total LY estimates when analysed separately in the current cost effectiveness assessment (response to Clarification Question B2).[11] The ERG requested the company to explore the influence of using different effectiveness estimates for docetaxel and methotrexate, based on CheckMate 141, in an exploratory analysis. Results were provided in the response to the clarification letter and are reported in Section 5.2.11.[11]

5.2.5 Perspective, time horizon and discounting

The analysis was conducted from the perspective of the NHS and PSS in England and Wales over a time horizon of 20 years. Costs and outcomes were discounted by 3.5%.

ERG comment: This is in line with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

Multiple parametric time-to-event models were used to estimate:

- overall survival (OS);
- progression-free survival (PFS) and;
- time to treatment discontinuation (TTD).

These were estimated based on the nivolumab arm and the investigator's choice (IC) arm of the CheckMate 141 trial. The estimated OS, PFS and TTD based on the IC arm were assumed to be applicable to docetaxel, methotrexate and paclitaxel (i.e. assuming equivalence among these treatments, as discussed in Section 5.2.4).

To estimate the time-to-event models, the following steps were followed (in accordance with NICE Decision Support Unit (DSU) guidance[55]):

1. Examine whether the proportional hazards assumption holds, based on log cumulative hazard plots. If this assumption does not hold, independent (i.e. stratified) models are estimated for the nivolumab and IC arms.
2. The following parametric survival distributions were examined using goodness-of-fit statistics and visual inspection:
    a. Exponential
    b. Weibull
    c. Gamma
    d. Gompertz
    e. Log-normal
    f. Log-logistic
    g. Generalised-gamma
    h. Spline models (using 1- and 2-knots)
3. Examine plausibility of the selected parametric survival distribution.

When selecting the parametric time-to-event models for nivolumab and IC, the company followed the NICE DSU guidance with respect to using the same statistical distribution in each treatment arm. Besides more traditional time-to-event models, the company also considered spline models for

representing OS, PFS and TTD. These models are more complex but more flexible than traditional time-to-event models. However, it has previously been suggested that when simpler parametric models provide sufficient fit to the data, these may be preferable to more complex spline models.[56] Therefore, the company only explored 1- and 2-knot spline models and examined whether the added complexity of spline models was justified.

For all three outcomes (OS, PFS and TTD), the proportional hazards assumption did not hold (CS Figures 23, 30 and 37; non-parallel curves that cross/overlap). Therefore, the company estimated all parametric time-to-event models independently for nivolumab and IC. The goodness-of-fit statistics for the parametric time-to-event models are presented in Table 5.5. In this Table, the lowest AIC/BIC is printed in bold and the company's preferred distribution is shaded (in case the distribution with the lowest AIC/BIC is a spline model, the lowest AIC/BIC for a non-spline model is also printed in bold).

Table 5.5: Summary of goodness-of-fit data

	OS		PFS		TTD	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Nivolumab						
Exponential	900.0974	903.5781	893.6523	897.1330	987.4401	990.9040
Weibull	902.0810	909.0423	888.9784	895.9397	986.2668	993.1944
Gamma	901.8304	908.7917	879.2260	886.1873	979.6614	986.5891
Gompertz	900.6289	907.5901	894.0397	901.0010	985.2420	992.1697
Log-normal	**892.7421**	**899.7033**	842.7126	849.6739	943.0808	950.0085
Log-logistic	895.9007	902.8619	**835.4127**	**842.3740**	**940.2247**	**947.1524**
Generalised-gamma	894.7097	905.1516	841.9505	852.3924	941.1387	951.5302
Spline models:						
1-spline hazard	894.5193	904.9612	821.8261	832.2680	926.0282	**936.4197**
1-spline odds	895.1440	905.5859	822.1553	832.5972	926.9783	937.3698
1-spline normal	894.6624	905.1043	839.8230	850.2649	939.1030	949.4945
2-spline hazard	896.0227	909.9452	814.7205	828.6430	925.6786	939.5340
2-spline odds	896.2647	910.1873	803.9737	817.8963	922.8006	936.6559
2-spline normal	896.6253	910.5478	**803.6091**	**817.5317**	**922.7013**	936.5566
IC						
Exponential	510.9038	513.6996	449.1393	451.9351	445.1522	447.8618
Weibull	502.4814	508.0729	424.9348	430.5264	418.3855	423.8045
Gamma	500.7490	506.3406	420.7156	426.3072	**416.0335**	**421.4525**
Gompertz	508.4971	514.0887	439.3768	444.9683	431.6542	437.0732
Log-normal	**500.0680**	**505.6596**	421.9280	427.5195	427.0343	432.4534
Log-logistic	500.2528	505.8444	**420.7133**	**426.3049**	418.9192	424.3382
Generalised-gamma	501.2385	509.6259	421.4421	429.8295	418.0262	426.1548
Spline models:						
1-spline hazard	501.6248	510.0121	421.3533	429.7407	418.1382	426.2668
1-spline odds	502.2196	510.6070	422.1099	430.4973	416.8364	424.9650
1-spline normal	501.0333	509.4206	421.2209	429.6083	416.6963	424.8249

	OS		PFS		TTD	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
2-spline hazard	503.5248	514.7080	423.3935	434.5767	418.2313	429.0694
2-spline odds	504.0737	515.2568	423.6595	434.8427	418.7268	429.5649
2-spline normal	503.0647	514.2479	423.0645	434.2477	418.0363	428.8744

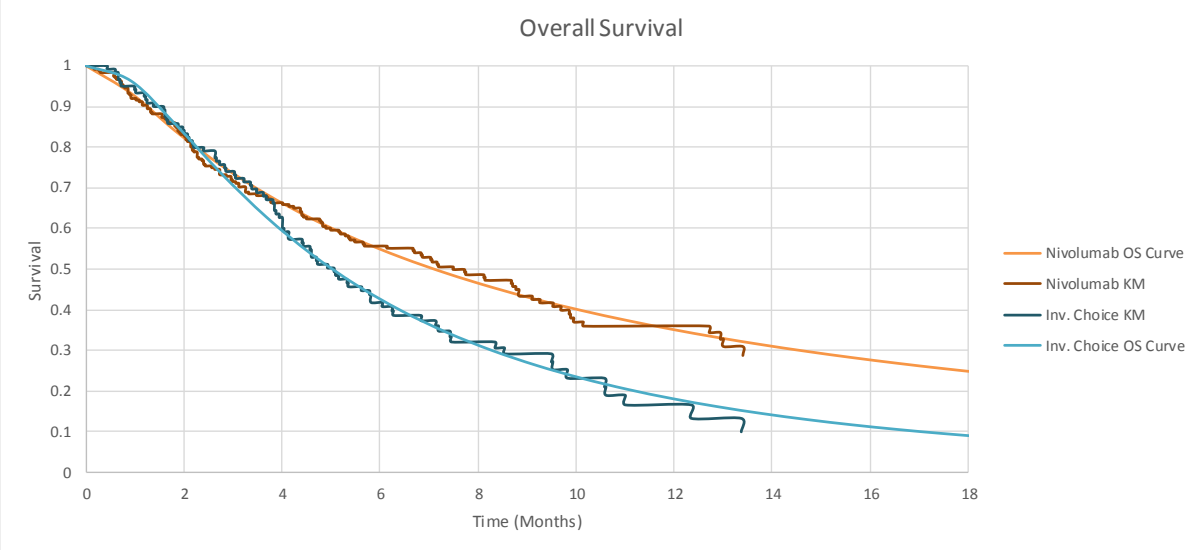
Source: Based on Tables 25, 26, 30, 31, 33 and 34 of the CS[1]
Note: the lowest AIC/BIC is printed in **bold** and the company preferred option is shaded in grey. In case the distribution with the lowest AIC/BIC is a spline model, also the lowest AIC/BIC for a non-spline model is printed in bold
AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CS = company submission; IC = investigator's choice; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation

Selection of distribution for overall survival

For OS, the log-normal distribution has the best goodness-of-fit statistics for both nivolumab and IC while the generalised-gamma distribution provides a similar goodness-of-fit fit for both treatment arms. The spline models were not considered further given that the added complexity was not justified based on the goodness-of-fit statistics. The company preferred the log-normal distribution based on the following arguments:

- The log-normal was the best fitting curve.
- Visual inspection indicated a satisfactory fit to the trial data (see Figure 5.2).
- The log-normal distribution produced estimates of OS that did not generate inconsistency with the long-term estimates of PFS and TTD.
- The estimated mortality probability remained higher than for the general population at all time points (as may be expected for this population).

Figure 5.2: OS Kaplan-Meier and log-normal curves



Source: Economic model submitted by the company; see also CS Figure 26[1]
CS = company submission; IC = investigator's choice; KM = Kaplan Meier; OS = overall survival

Plausibility of selected distribution for the extrapolation of overall survival

To examine the plausibility of the OS extrapolation, the company compared the estimated OS for R/M SCCHN patients treated with nivolumab based on the log-normal distribution with OS observed in

squamous cell non-small cell lung cancer (NSCLC) treated with nivolumab (CheckMate 017, 063 and 003 trials[57-59]). The extrapolated OS estimates of R/M SCCHN patients using the log-normal curve provided two and three year OS estimates of 18.8% and 11.9% respectively while two and three year OS estimates observed in squamous cell NSCLC patients were 23%-35% and 28% respectively (CS Table 28 and CS Figure 27).[1] Moreover, the annual survival probability for squamous cell NSCLC treated with nivolumab (CheckMate 017 and 003 trials[57, 58]) was compared with the extrapolated survival probability based on the log-normal distribution (Table 5.6). This shows that the modelled annual survival probability is consistently lower than those observed in the squamous cell NSCLC clinical studies (this is also illustrated in CS Figure 29).[1]

Table 5.6: Validation of estimated OS for nivolumab

Months	Annual survival probability		
	log-normal distribution based on CheckMate 141	Checkmate 003 (squamous cell NSCLC)	Checkmate 017 (squamous cell NSCLC)
12	35%	49%	42%
24	53%	71%	54%
36	63%	80%	
48	69%		
Source: Based on Figure 28 of the CS[1] CS = company submission; NSCLC = non-small cell lung cancer; OS = overall survival			

The company did not find an appropriate data source for validating the OS estimated for the IC arm. Hence, the company relied on clinical expert opinion indicating that 1, 2 and 4 year survival would be 10-20%, 5% and 1-2% respectively. This aligned well with the estimated OS for IC based on the log-normal distribution, which were 18.1%, 5.1%, 2.0% and 0.9% for years 1-4 respectively (see Table 5.7 and CS Table 29).[1] The estimated yearly survival probabilities using the log-normal distribution are provided in Table 5.7 for both treatment arms. Moreover, Table 5.8 displays the mean OS estimated using all survival distributions considered relevant by the company.

Table 5.7: Estimated OS for nivolumab and IC (based on log-logistic distribution)

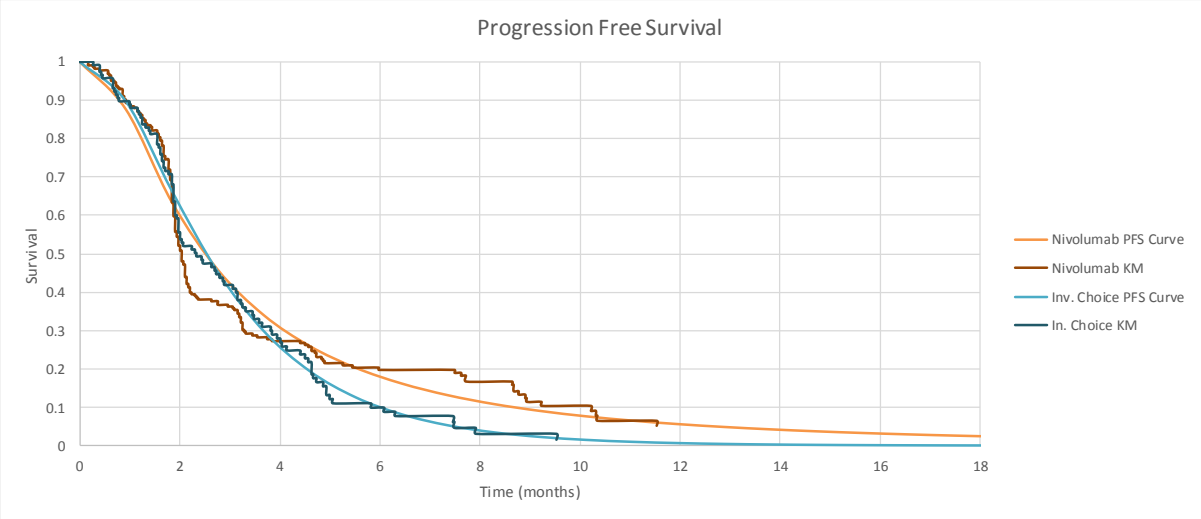
Months	OS		
	Nivolumab	IC	Difference
12	35.2%	18.1%	17.0%
24	18.8%	5.1%	13.7%
36	11.8%	2.0%	9.9%
48	8.2%	0.9%	7.3%
60	6.0%	0.5%	5.5%
120	2.0%	0.0%	1.9%
180	0.9%	0.0%	0.9%
240	0.5%	0.0%	0.5%
Source: Economic model submitted by the company IC = investigator's choice; OS = overall survival			

Selection of distribution for progression-free survival

For PFS, the 2-spline normal model has the best goodness-of-fit statistics for the nivolumab arm while the best non-spline model was the log-logistic distribution (see Table 5.5). For the IC arm, the log-logistic distribution has the best goodness-of-fit statistics with the gamma, log-normal, generalised-gamma and 1-spline models having a similar goodness-of-fit. The company stated that there was no clear best fitting distribution and hence further considered the following distributions as its base-case: the 2-spline odds (as well fitting for nivolumab), the log-logistic (as best fitting for the IC arm) and the generalised-gamma and log-normal (as well fitting for both arms).

The company stated that none of the distributions had a particularly strong fit to the nivolumab Kaplan-Meier curve. Moreover, the company did not regard the estimated PFS using the 2-spline odds model for nivolumab as plausible (Table 5.8). Based on visual inspection, the company stated that it preferred the generalised-gamma distribution over the log-logistic or log-normal distribution for both nivolumab and IC (Figure 5.3).

Figure 5.3: PFS Kaplan-Meier and generalised-gamma curves



Source: Economic model submitted by the company; see also CS Figure 33[1]
CS = company submission; IC = investigator's choice; KM = Kaplan Meier; PFS = progression-free survival

Plausibility of selected distribution for the extrapolation of progression-free survival

The company mentioned that it was reassuring that the PFS curves remained below the OS curve (CS Section 5.7.2) and that the predicted mean PFS is aligned with expert clinical opinion (CS Section 5.10). Other than this, the company did not report on the plausibility of the generalised-gamma distribution for the extrapolation of PFS.

Selection of distribution for time to treatment discontinuation

For nivolumab, the best-fitting models for TTD were the spline models (notably the 2-spline odds and 2-spline normal; see Table 5.5). Of the non-spline models, the log-logistic distribution was the best fitting, followed by the generalised-gamma distribution. For IC, the best fitting curve was the generalised-gamma distribution. Therefore, the company considered the 2-spline odds, 2-spline normal, generalised-gamma and log-logistic distributions for its base-case.

The company stated that, based on visual inspection of the TTD distributions against the Kaplan-Meier trial data, there were no clear choices for a potential base-case distribution. The mean TTD estimated using different distributions highlighted that whilst the choice of distribution for the IC arm had little effect on mean TTD, the choice of distribution for nivolumab had a considerable influence on mean

TTD estimates (Table 5.8). The 2-spline models were not considered plausible by the company as these models estimated that approximately 5% of patients are still on treatment at four years, which is inconsistent with expert clinical opinion indicating an absolute maximum treatment duration of three years.[51] Moreover, the 2-spline models were considered incompatible with the models used to estimate OS and PFS. The company concluded that the log-logistic distribution had a slightly better statistical fit than the generalised-gamma distribution for both nivolumab and IC and was therefore chosen as the base-case distribution for TTD (Figure 5.4).

Figure 5.4: TTD Kaplan-Meier and log-logistic curves

Source: Economic model submitted by the company; see also CS Figure 38[1]
CS = company submission; IC = investigator's choice; KM = Kaplan Meier; TTD = progression-free survival

Plausibility of selected distribution for the extrapolation of time to treatment discontinuation
The company mentioned that it was reassuring that the TTD curves remained below the OS curve (CS Section 5.7.2) and that the predicted mean TTD is aligned with expert clinical opinion (CS Section 5.10). Other than this, the company did not report on the plausibility of the log-logistic distribution for the extrapolation of TTD.

Table 5.8: Estimated mean OS, PFS and TTD in months (over a time horizon of 20 years)

	Mean OS (months)		Mean PFS (months)		Mean TTD (months)	
Distribution	**Nivolumab**	**IC**	**Nivolumab**	**IC**	**Nivolumab**	**IC**
Exponential	11.2	7.8	[b]	[b]	[b]	[b]
Weibull	11.2	7.0	[b]	[b]	[b]	[b]
Gamma	11.0	7.1	[b]	[b]	[redacted][b,c]	3.3[b,c]
Gompertz	21.0	6.9	[b]	[b]	[b]	[b]
Log-normal	17.7	8.4	4.3	3.7	[b]	[b]
Log-logistic	18.7	9.1	4.3	3.9	[redacted]	3.6

	Mean OS (months)		Mean PFS (months)		Mean TTD (months)	
Distribution	**Nivolumab**	**IC**	**Nivolumab**	**IC**	**Nivolumab**	**IC**
Generalised-gamma	18.6	7.6	4.6	3.6	[redacted]	3.3
Spline models:						
1-spline hazard	[a]	[a]	[b]	[b]	[b]	[b]
1-spline odds	[a]	[a]	[b]	[b]	[b]	[b]
1-spline normal	[a]	[a]	[b]	[b]	[b]	[b]
2-spline hazard	[a]	[a]	[b]	[b]	[b]	[b]
2-spline odds	[a]	[a]	9.2	3.7	[redacted][d]	3.3[d]
2-spline normal	[a]	[a]	7.6[b,c]	3.6[b,c]	[redacted]	3.3

Source: Based on Tables 27, 32 and 35 of the CS[1]

Note: The company preferred option is shaded in grey; [a] The spline models were not considered relevant given that the added complexity was not justified based on the goodness-of-fit statistics; [b] This distribution was not considered relevant by the company; [c] Added by the ERG as this distribution had the best goodness-of-fit statistics for at least one treatment; [d] Corrected by the ERG (recalculated based on the economic model submitted by the company)

CS = company submission; ERG = Evidence Review Group; IC = investigator's choice; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation

ERG comment: The ERG considered the statistical methods used by the company for selecting the distributions for the time-to event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis.[55] This includes the preference for using the same distribution for nivolumab and IC. However, the ERG has some issues with the interpretation and validation of the selected time-to-event models. Moreover, the ERG questions the assumption of equivalence between docetaxel and methotrexate as well as docetaxel and paclitaxel (see Section 4 and Section 5.2.4 for more details). Finally, it should be noted that the coefficients for the various time-to-event models and the formulas to implement these into the economic model were not provided in the CS or original economic model, but were provided upon request in response to the clarification questions (albeit this was not provided for the spline model).[11]

The ERG agrees with the selection of the log-normal distribution for OS. For PFS, the ERG questioned (clarification question B4) whether the company could have used the log-normal distribution in its base-case (as the statistically best fitting distribution) instead of the company preferred generalised-gamma distribution (based on visual inspection). After further clarification by the company, and additional visual inspection by the ERG, the generalised-gamma distribution was considered reasonable by the ERG, also considering the relatively low impact this choice has on the ICER (see clarification response Table 24[11]). The ERG did, however, consider the selection of the log-logistic distribution for TTD by the company to be suboptimal and used the generalised-gamma distribution in the ERG base-case for two reasons. Firstly, the PFS and TTD curves cross for the IC arm suggesting that there is post-progression treatment which seems implausible for the IC arm; using the generalised-gamma distribution would resolve this issue (see Figure 5.5). Secondly, although there is no clear best option based on the goodness-of-fit statistics, based on visual inspection the ERG would prefer the generalised-gamma distribution, as the tail seems more plausible given the shape of the KM (see Figures 5.4 and 5.6).

Figure 5.5: OS, PFS and TTD curves (company base-case, ERG base-case)

Company base-case (log-logistic distribution for TTD) - nivolumab

ERG base-case (generalised-gamma distribution for TTD) - nivolumab

Company base-case (log-logistic distribution for TTD) - IC

ERG base-case (generalised-gamma distribution for TTD) - IC

PFS = progression-free survival; TTD = progression-free survival

Figure 5.6: TTD Kaplan-Meier and generalised-gamma curves

Source: Economic model submitted by the company
IC = investigator's choice; KM = Kaplan Meier; TTD = progression-free survival

The ERG questioned the assumption of equivalence between docetaxel and methotrexate and requested treatment specific analyses for docetaxel and methotrexate to inform OS, PFS and TTD (instead of equal effectiveness based on the IC). These analyses were provided by the company in response to clarification question B2.[11] The results of using treatment specific time-to-event models seem to support the notion that the group of patients for whom the (intended) investigator's choice was docetaxel differ from those for whom the (intended) investigator's choice was methotrexate (e.g. in terms of total LYs). However, the incremental costs and QALYs and thus also the ICER based on these analyses were comparable to the company base-case (see clarification response Table 22[11]). The ERG would ideally prefer to use treatment specific effectiveness estimates in its base-case. However, the ERG decided not to incorporate this in its base-case, taking the following considerations into account:

- The time-to-event curves used by the company to inform the analyses using treatment specific OS, PFS and TTD lack face validity as the OS curve falls below PFS curve (leading to negative numbers in the Markov trace) for both docetaxel and methotrexate. Additionally, for methotrexate the OS curve also falls below the TTD curve (suggesting treatment for patients that have deceased).
- Using nivolumab (based on patients for whom the intended choice was docetaxel) versus docetaxel and paclitaxel and nivolumab (based on patients for whom the intended choice was methotrexate) versus methotrexate would have made it difficult to consider all comparators in one incremental analysis. This is caused by the fact that in that case the outcomes for the nivolumab group (LY, QALYs, costs) would be different for the two comparisons.
- The incremental results are comparable to the company base-case.

5.2.7 Adverse events

The impact of adverse events (AEs) on costs and utility was incorporated in the first cycle of the model (once only). Any all-cause Grade 3 or 4 AE were included if the incidence was ≥5% in either

arm of the CheckMate 141 trial. Subsequently clinical expert opinion was sought to validate these AEs and to confirm that no AEs with a meaningful cost or disutility had been omitted using these criteria. Based on clinical expert feedback dysphagia, nausea and vomiting and anorexia were incorporated as well (Table 5.9).

Table 5.9: All-cause Grade 3 or 4 adverse events that were included in the model

Adverse event, n (%)	Incidence in CheckMate 141		Justification for inclusion
	Nivolumab (n=236)	IC (n=111)	
Fatigue	8 (3.4%)	7 (6.3%)	Incidence of ≥5% in either arm of CheckMate 141
Dyspnoea	13 (5.5%)	2 (1.8%)	
Hyponatraemia	11 (4.7%)	9 (8.1%)	
Anaemia	14 (5.9%)	9 (8.1%)	
Neutropenia	0 (0.0%)	8 (7.2%)	
Dysphagia	9 (3.8%)	3 (2.7%)	Identified by UK clinicians as being relevant to patients
Nausea and vomiting	2 (0.8%)	1 (0.9%)	
Anorexia[a]	3 (1.3%)	4 (3.6%)	

Source: Based on Table 37 of the CS[1]
Note: [a] Reported as decreased appetite
CS = company submission; IC = investigator's choice; UK = United Kingdom

ERG comment: The ERG questioned the use of the 'once only' approach to incorporate the impact of AEs on costs and QALYs. In response to clarification question B5,[11] the company indicated that this is a pragmatic approach and that was used to prevent additional complexity in the model, also in relation to the potential impact on the incremental outcomes. The ERG requested the company to incorporate the impact of AEs over time in a scenario analysis, but the company did not provide this scenario analysis. The ERG considers the 'once only' approach not to be in line with best practices but does not regard this as a priority issue because the impact on the incremental outcomes is most likely minimal.

Treatment-related 'select' AEs from the CheckMate 141 trial with a potential immunological cause that are of special clinical interest with the use of nivolumab (CS Table 21) were not incorporated in the economic model due to the low frequencies of occurrence.[1] However, in response to the clarification letter, the company added pneumonitis as an AE (which was also included in the appraisal of nivolumab in metastatic renal cell carcinoma; ID853). Pneumonitis will also be included as AE in the ERG base-case.

5.2.8 Health-related quality of life

The systematic literature review (SLR) on HRQoL only identified one study of potential relevance.[60] In this study, utilities were derived from members of the Canadian general public using the standard gamble approach for a variety of health states related to head and neck cancer (including recurrent or metastatic disease; CS Appendix 10).[60] Hence, in the absence of any published, UK-specific, utility data that were elicited using methods preferred by NICE, utility data from the CheckMate 141 trial were considered to be most relevant to the decision problem for this appraisal.

EQ-5D-3L data from the CheckMate 141 trial

Treatment-dependent health state utilities for the progression-free and progressed disease states were derived from the EQ-5D-3L data collected from patients in the CheckMate 141 trial. Patient-level EQ-

5D-3L responses from the CheckMate 141 trial were converted to utility index-based scores using the UK-specific scoring algorithm published by Dolan 1997.[61] The assessment date of each EQ-5D-3L was compared to the date of RECIST-defined progression. In the CS, patients included in the analysis consisted of the randomised population (n=361) that had any non-missing EQ-5D-3L and tumour response data. This information was available for a total of [redacted] patients in the nivolumab group and [redacted] patients in the IC group.[62] Accounting for those patients who contributed multiple observations, a total of [redacted] and [redacted] observations were obtained in the nivolumab group and IC group, respectively.[62] Note that whilst some patients had multiple measurements, the EQ-5D-3L measurements were assumed to be independent (i.e. neglecting within-subject correlation).

Data for both EQ-5D-3L and tumour response in [redacted] were completely missing (i.e. unable to calculate a utility score at any time point/stratified for tumour response). The health-state utilities derived from the EQ-5D-3L data obtained in the CheckMate 141trial are provided in Table 5.10.

Table 5.10: Health-state utilities derived from the EQ-5D-3L obtained in the CheckMate 141 trial

Health state	Nivolumab		IC of therapy		Overall	
	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]	N	Mean utility value (SD) [95% CI]
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 38 of the CS,[1] Bristol-Myers Squibb – Analysis of Quality-of-Life Endpoints in CheckMate 141. Data on File No.: OR NIVO 059[62]

Note: N = Number of observations, corresponding to the total number of EQ-5D-3L responses across all patients in that progression state who contributed at least one EQ-5D-3L response.

CI = confidence intervals; CS = company submission; EQ-5D-3L = 3-level EuroQoL-5 Dimensions; IC = investigator's choice; SD = standard deviation

The company acknowledged that HRQoL estimates might be based on a self-selected population of patients who were well enough to complete forms. Hence this may be a concern for possibly biased estimates. To address this concern, completion rates for the EQ-5D-3L questionnaire in CheckMate 141 were examined (see Table 5.11 for more details). Similar to the other PROs assessed in CheckMate 141, fewer than [redacted] patients in the IC arm were eligible for on-treatment assessment using the EQ-5D-3L after week 21.[63] Moreover, to explore the possibility of bias, EQ-5D data solely from the first 21 weeks of the trial (CS Table 40) were explored by the company to identify whether there was evidence of lower average PF utility scores with this earlier time-point cut-off. For this analysis there were a total of [redacted] and [redacted] respondents included in the nivolumab group and IC group, respectively.[62] This corresponded to a total of [redacted] observations in the nivolumab group and [redacted] observations in the IC group in the PF state. Based on the interpretation of this analysis, the company suggested that PF utility scores with and without the 21 week restriction were similar (CS Tables 38 and 40) and hence that the utility values reported in Table 5.12 are reliable.

Table 5.11: EQ-5D-3L questionnaire completion rate summary from CheckMate 141

Time point	Nivolumab (n=240)		IC (n=121)	
	N[a]	n (%)[b]	N[a]	n (%)[b]
Baseline	240	191 (79.6)	121	90 (74.4)
Week 9	131	103 (78.6)	57	35 (61.4)
Week 15	85	58 (68.2)	30	16 (53.3)
Week 21	58	48 (82.8)	14	7 (50.0)
Week 27	44	31 (70.5)	5	2 (40.0)
Week 33	30	21 (70.0)	3	2 (66.7)
Week 39	19	9 (47.4)	1	1 (100)
Week 45	15	11 (73.3)	0	0
Week 51	9	6 (66.7)	0	0
Week 57	5	3 (60.0)	0	0
Week 63	2	0 (0)	0	0
Week 69	2	2 (100)	0	0
Follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 39 of the CS, Bristol-Myers Squibb – Additional Analyses of Data Collected in CheckMate 141. Data on File No.: OR NIVO 058[63]

Notes: a N = Number of subjects in study; b n = Number of questionnaires received; % = completion rate, where completion is defined as a non-missing response in at least 1 of EQ-5D dimensions: Mobility, Self Care, Activity, Pain, Anxiety and VAS; Follow-Up Visit 1 was scheduled for 35 days from the last dose ±7 days or coincided with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose. Follow-Up Visit 2 was scheduled for 80 days (±7 days) from Follow-Up Visit 1; Survival Follow-Up visits were scheduled for every 3 months after Follow-Up visit 2.

CS = company submission; EQ-5D-3L = 3-level EuroQoL-5 Dimensions; IC = investigator's choice; VAS = visual analogue scale

Adverse event utility decrements

In the CS, the utility decrements were applied separately for each AE and were applied once during the first cycle of the model, based on the proportion of patients in each treatment arm experiencing each AE (see CS Section 5.3.6). Due to a lack of published disutility values for AEs in SCCHN specifically, disutility estimates were obtained from studies and previous technology appraisals reporting disutility estimates from patients with advanced lung cancer and gastrointestinal malignancies (see Table 5.12).[64, 65] The use of utility data from these indications was validated by a UK clinical expert. The company stated that the utility values from TA 172 (CS Table 41) were comparable. No disutility value was available for hyponatraemia, and a disutility of zero was assumed. For anaemia, no disutility was

reported; this disutility estimate was assumed to be the same as that of fatigue, based on expert clinical opinion.

In the CS it was stated that the health state utility values presented (CS Section 5.4.1) were treatment-specific and therefore implicitly captured the utility impact of AEs experienced on therapy. The company indicated that applying the disutilities for AEs (CS Table 42) may result in double-counting of the disutility associated with AEs experienced on treatment. Therefore, a scenario analysis was conducted in which the disutility values for all AEs were set to zero (see CS Scenario 13; Section 5.8.3). In addition, a scenario analysis was conducted to explore the impact of assuming no differential health state utility between nivolumab and IC by using health state utilities for the overall trial population from the CheckMate 141 for all therapies in the model (see CS Scenario 12; Section 5.8.3).

Table 5.12: Summary of the health-related quality of life estimates used in the CS

Health State	(Dis-)Utility value*: mean (SD)	95% CI	Justification
Nivolumab**			
Progression-free	[redacted]	[redacted]	Derived from patient-level EQ-5D-3L data collected in CheckMate 141[62]
Progressed disease	[redacted]	[redacted]	
IC of therapy**			
Progression-free	[redacted]	[redacted]	Derived from patient-level EQ-5D-3L data collected in CheckMate 141[62]
Progressed disease	[redacted]	[redacted]	
Death	0	-	
All cause Grade 3 or 4 AE with ≥5% incidence**			
Fatigue	-0.07346	-	Derived from published study in advanced lung cancer – lack of data for this AE in SCCHN, specifically
Dyspnoea	-0.05	-	Derived from published study in advanced lung cancer – lack of data for this AE in SCCHN, specifically
Hyponatraemia	0	-	Conservative assumption (lower incidence with nivolumab versus IC)
Anaemia	-0.07346	-	Assumed to be same as fatigue, as per previous appraisal
Neutropenia	-0.08973	-	Derived from published study in advanced lung cancer – lack of data for this AE in SCCHN, specifically
Dysphagia	-0.04802	-	Assumed to be the same as for nausea and vomiting
Nausea and vomiting	-0.04802	-	Derived from published study in advanced lung cancer – lack of data for this AE in SCCHN, specifically
Anorexia	-0.153	-	Based on previous appraisal

Source: Based on Sections 5.3.6 and 5.4.1 of the CS[1]

Notes: * Utility values for progression-free, progressed disease and death (subheadings "Nivolumab" and "IC of therapy"), Disutilites values for "All cause Grade 3 or 4 AE with ≥5% incidence" ** Health-state utility data from the overall CheckMate 141 population were also used in a scenario analysis assuming treatment

Health State	(Dis-)Utility value*: mean (SD)	95% CI	Justification
independent utility scores (Scenario 12), mean (SD) [95% CI]: PF = [redacted][62]			

AE = adverse event; CI = confidence intervals; CR = complete response; CS = company submission; EQ-5D-3L = 3-level EuroQoL-5 Dimensions; NSCLC = non-small cell lung cancer; PD = progressed disease; PF = progression-free; SCCHN = squamous cell carcinoma of the head and neck; SD = standard deviation

ERG comment: In response to the clarification question B6, the company indicated that the 'select' AEs as presented in CS Table 21 (AEs with a potential immunological cause that are of special clinical interest with the use of nivolumab) were rare in both nivolumab and IC arms of the CheckMate 141 trial. The rates of these AEs in the nivolumab and IC arms of the model are provided in the response to the clarification letter ([redacted]).[11] The frequency of occurrence of 'select' AEs was below the 5% criterion for selection of grade 3-4 events and thus the company felt that the justification to include these AE was limited. The company performed pragmatic searches but was unable to identify costs or utility estimates for any of the 'select' AEs except for pneumonitis, which was included in prior/ongoing NICE appraisals of nivolumab for lung cancer and renal-cell carcinoma indications. The cost and utility decrement associated with pneumonitis episode were estimated to be £418.91 and -0.15 (see clarification letter Table 25).[11] The company added a scenario analysis in which pneumonitis was included. This (with and without PAS) had a negligible impact on the overall ICER (see clarification letter Table 26 and Table 27).[11] Nevertheless, the ERG considered pneumonitis a potentially relevant AE and was therefore included in the ERG base-case.

Treatment-dependent health state utilities for the progression-free and progressed disease states were derived from the EQ-5D-3L data collected from patients in the CheckMate 141 trial. However, data for both EQ-5D-3L and tumour response in [redacted] of 361 patients ([redacted]) were missing. In response to the priority question B7 of the CL, the company identified [redacted] patients who had a baseline EQ-5D score but were not assigned to a health state at baseline and hence were not included in the CS. The company repeated the calculation of utility values by therapy and by health state including these [redacted] patients, under the assumption that these patients were in the pre-progression health state at the time of the baseline measurement (consistent with the inclusion criteria). Table 5.13 presents the results of the recalculation of the utility values including these [redacted] patients, which were also used in the ERG base-case as the ERG prefers to use all available baseline utility data. However, in these analyses there are still [redacted]/361 patients with missing data.

Table 5.13: Updated utility values with additional baseline EQ-5D assessments allocated as pre-progression

	Nivolumab		IC of therapy		Overall	
Health state	**N**	**Mean utility value (SD) [95% CI]**	**N**	**Mean utility value (SD) [95% CI]**	**N**	**Mean utility value (SD) [95% CI]**
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 29 of the response to the request for clarification[11]

	Nivolumab		IC of therapy		Overall	
Health state	**N**	**Mean utility value (SD) [95% CI]**	**N**	**Mean utility value (SD) [95% CI]**	**N**	**Mean utility value (SD) [95% CI]**
CI = confidence interval; EQ-5D = European Quality of Life-5 Dimensions; SD = standard deviation						

After adding the [redacted] patients missing in the original analysis, the progression-free utility estimates were lower for both nivolumab and IC. The company provided a scenario analysis in which these adjusted treatment-specific health-state utility values were used (see response to request for clarification Tables 30 and 31).[11] The results of this scenario shows that ICERs of nivolumab compared with IC remained approximately in the same range when compared with the CS base-case (prior to the inclusion of [redacted] missing patients).

Additionally, the company indicated that a high proportion of patients dropped out of the assessments before week 27 (see Table 5.14). The reasons for patient dropout were mainly death and cases of disease progression. The company stated that other reasons for missing data were not collected in the trial.

Table 5.14: Missing patient data patterns

Number of EQ-5D-3L utility index (UK weights), Assessments by Visit (N=347)				
Analysis Visit	**Number of missing**	**Cumulative Number of deaths**	**Cumulative Number of disease progressions**	**Cumulative Number of deaths & disease progressions**
0	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]
39	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]
51	[redacted]	[redacted]	[redacted]	[redacted]
57	[redacted]	[redacted]	[redacted]	[redacted]
63	[redacted]	[redacted]	[redacted]	[redacted]
69	[redacted]	[redacted]	[redacted]	[redacted]
Source: Based on Table 32 of the response to the request for clarification[11] EQ-5D-3L = European Quality of Life-5 Dimensions, three-level scale; UK = United Kingdom				

In response to priority question B7c of the CL, the company carried out multiple imputation (MI) to address missingness (Table 5.14) using a principled method, rather than the naïve available cases approach that was used in the CS. The imputation model used age group, ECOG performance status, smoking status and prior chemotherapy as the explanatory variables. The imputation was run (10 imputations) without including treatment arm in the imputation model and then repeated by treatment arm. The results of the utility analysis using the imputation method described above are presented in Table 5.15 (for the IC arm and for the nivolumab arm).

Table 5.15: Imputation (pooled visits)

Parameter estimates (10 imputations)									
IC	**Mean**	**SE**	**95% confidence limits**		**Nivolumab**	**Mean**	**SE**	**95% confidence limits**	
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	**Pre-progression**	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	**Post-progression**	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Tables 33 and 34 of the response to the request for clarification[11]
IC = investigator's choice; SE = standard error

From these results, we see that the MI approach (Table 5 15) leads to vastly different results than the available cases approach (Table 5.13). Most striking is that in the MI estimates, the pre-progression utility of IC is higher than that for nivolumab, which is exactly the reverse from the available cases results. For the post-progression state, the utility in the nivolumab group is the highest regardless of the analysis approach, but the MI estimates lie much closer together. Thus, it would be expected that the ICERs would increase when the MI derived utility estimates are used for the model calculations. This is indeed what is observed in the results presented in the response to the clarification letter: without PAS, [redacted] and with PAS the ICERs changed from about £35,000 to about £41,000. This increase corresponds to a difference of approximately 15% on the ICERs.

In their response to the request for clarification, the company made clear that although the utility values presented in the CS were validated with clinicians, the utilities estimated after the imputation were not.[11] They also indicated that in their opinion the most appropriate utility values to use in the base-case of the cost effectiveness model were those provided in Table 5.13.

The company listed various caveats for the multiple imputation approach in their response to the request for clarification. However, it is the ERG's opinion that the available cases analysis, as was used in the CS, also has its flaws, most notably the potential bias due to missing cases (illustrated by the MI results) and the underestimation of uncertainty. This is because the uncertainty due to missingness is disregarded with naïve imputation methods. But overall, the ERG agrees with the company that the multiple imputations as applied in the response to clarification letter cannot be considered robust. Specifically, during the imputation, a very limited set of explanatory variables for missingness was used, despite the fact that the assumption of data being missing-at-random becomes more likely as more exploratory variables are included. Hence, the current list seems unnecessarily restrictive. Also, the ERG questions the approach of first pooling over time, since this approach only imputes values for patients who had zero observations instead of imputing also values for those who had some, but not all observations. Moreover, it is clear from Table 5.14 that there is a non-negligible number of patients becoming true missing, rather than progressing or dying.

Based on the fact that the observed cases estimates and MI estimates are vastly different, combined with the problems with the MI procedure and the lack of overall (treatment independent) MI estimates of utility, the ERG has decided to use the utility estimates provided in Table 5.13 for the ERG base-case that will be presented in Section 5.3. However, instead of following the approach employed by the company, using treatment-specific utility values for each health state, the overall treatment independent utility values will be used. It is unclear to the ERG whether the differences in utility between the treatments are due to the differences between the treatments or the selection of cases (i.e. missing cases). The ERG approach will avoid double counting of the impact of treatment-related adverse events.

5.2.9 Resources and costs

Resource use and costs included in the CS model were based on data from the CheckMate 141, previous technology appraisals and published sources identified in the SLR.

Resource identification, measurement and valuation studies

The SLR identified a total of 38 studies that reported cost/resource use data for the treatment of SCCHN (see CS Appendix 11). Of these, one UK study reported relevant data for inclusion in the cost effectiveness analysis. In the absence of any additional sources of evidence, assumptions were made for both cost and resource inputs included in the model, where necessary, and were validated by expert clinical opinion.[9, 52]

Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs were obtained from the British National Formulary (BNF 2016[66]) for nivolumab and from the electronic market information tool (eMIT 2015[67]) for IC drugs. A PAS has been agreed for nivolumab whereby a confidential discount was applied to the cost per vial (100 mg or 40 mg). The outcomes in the CS were presented with and without the PAS applied to the acquisition cost for nivolumab.

Dose frequency – weight, body surface area and dose delays

The dosing frequency of nivolumab, docetaxel and methotrexate used in the base-case analysis was based on the schedule followed in the CheckMate 141 trial (nivolumab: 3 mg/kg, Q2W intravenous (i.v.), docetaxel: 30 mg/m^2, QW i.v., methotrexate: 40 mg/m^2, QW i.v.). Nivolumab dose was calculated based on body weight in kilograms (kg). The dosages for docetaxel, paclitaxel and methotrexate were calculated based on body surface area (BSA). Mean weight and BSA were based on the population of European patients reported in CheckMate 141 ([redacted], respectively). This was based on an assumption that the European patients were more likely to reflect the weight and BSA characteristics of the UK population than the trial population.[63] The weight and BSA inputs based on UK patients included in CheckMate 141 were not used in the base-case due to the small sample size (n=34).[63] However, scenario analyses were conducted using the weight and BSA inputs for the whole trial population (see CS Scenario 20 in Section 5.8.3) and using the BSA from a retrospective study of UK cancer patients, specifically including head and neck patients (see CS Scenario 21 in Section 5.8.3).[68]

For the use of weight, a normal distribution was assumed by the company, based on lack of evidence and for alignment with the distribution applied for BSA.[68] These distributions were derived from the mean and SD values from CheckMate 141 given above and were used to estimate the proportion of patients requiring each possible number of vials. In the CS base-case analysis, no vial sharing was assumed for all therapies. The use of vial sharing was included in a scenario analysis (see CS Scenario 15 in Section 5.8.3). A reduction in dose intensity was included in the base-case based on the proportion of doses received that were delayed in CheckMate 141.[25] Dose intensity was estimated to be [redacted] for nivolumab, docetaxel and methotrexate, respectively. This calculation relied on the assumption that a dose delay was equivalent to a single missed dose for nivolumab (Q2W), methotrexate or docetaxel (QW for both) – in CheckMate 141 (i.e. the drug cost would not be incurred by the NHS), the average dose delay was [redacted] days for nivolumab, [redacted] days for methotrexate and [redacted] days for docetaxel.[63]

A scenario analysis was conducted in which no reductions in dose intensity were assumed (i.e. 100% dose intensity; see CS Scenario 16; Section 5.8.3). In addition, it was stated that the dosing frequency of docetaxel that is most routinely used in UK clinical practice was 75 mg/m^2, once every three weeks. In a scenario analysis, costs associated with this dosing frequency for docetaxel were applied to the

model, by using the same reductions in dose intensity modelled as for the QW regimen (see CS Scenario 14; Section 5.8.3). The use of the 30 mg/m^2, once weekly schedule in the base-case analysis was chosen to ensure consistency with the trial regimen from which efficacy and safety inputs for the model were derived.

Paclitaxel, which was not included as a treatment option in the IC arm of CheckMate 141, was included in the model at a dosage of 80 mg/m^2 QW, based on the dose that is most frequently used by practicing clinicians in the UK (paclitaxel: 80 mg/m^2 QW i.v.).[9, 52] The reduction in dose intensity calculated for docetaxel 30 mg/m^2, QW ([redacted]) was also applied to paclitaxel QW, in the absence of data for paclitaxel 80 mg/m^2, QW, specifically.

Drug acquisition costs for nivolumab and IC included in the model are presented in Table 5.16.

Table 5.16: Drug acquisition costs – assuming wastage

Treatment	Dose required	Unit (vial)	Cost per vial	Cost per dose (weighted average)*	Doses per cycle	Cost per cycle
Nivolumab (without PAS)	3 mg/kg, Q2W	100 mg	£1,097.00	[redacted]	2	[redacted]
		40 mg	£439.00			
Nivolumab (with PAS)	3 mg/kg, Q2W	100 mg	[redacted]	[redacted]	2	[redacted]
		40 mg	[redacted]			
Docetaxel	30 mg/m^2, QW	80 mg	£12.47	£12.47	4	£49.88
Paclitaxel	80 mg/m^2, QW	100 mg	£8.50	£17.21	4	£68.84
Methotrexate	40 mg/m^2, QW	500 mg	£12.19	£12.19	4	£48.76

Source: Based on Table 44 of the CS[1]
Note: *Adjusted for patient distributions of weight (nivolumab) and BSA (docetaxel, paclitaxel and methotrexate); eMIT 2015 for docetaxel, paclitaxel and methotrexate formulations and list price; BNF for nivolumab formulation and list price
BNF = British National Formulary; BSA = body surface area; eMIT = electronic market information tool; Q2W = once every two weeks; QW = once weekly

Drug administration and monitoring costs
The costs of drug administration and monitoring for the nivolumab, docetaxel, paclitaxel, and methotrexate included in the model are presented in CS Section 5.5.2, Table 45. Costs were derived from the NHS reference cost schedule 2014–15.[69] All therapies included in the model are intravenously-administered and therefore assumed to incur the same administration costs.

The type and frequency of monitoring visits were assumed to be the same for all patients included in the model who were receiving initial systemic therapy. For patients who had discontinued initial systemic therapy, monitoring costs were assumed to decrease to an oncologist visit with cell blood count every 12 weeks (see CS Table 45).

Subsequent systemic therapy
In the base-case analysis, the proportion of patients who received subsequent systemic therapy post-discontinuation was based on the CheckMate 141 (nivolumab [redacted] and IC [redacted], see CS Table 46).[1, 25] In the CS, it was assumed that patients would only receive one additional systemic therapy post-discontinuation. Data on the duration of subsequent treatment was not directly available from the

CheckMate 141 trial. The company assumed that patients would receive subsequent therapy for a median of 1.9 months. This assumption was justified by the median duration of therapy for patients in the IC arm of CheckMate 141, presented in CS Section 4.12.[1] This assumption was considered plausible by clinical experts.[51]

Other assumptions included that patients who had received either docetaxel or paclitaxel were not treated with another taxane. Hence, for the docetaxel or paclitaxel treatment arms, it was assumed that patients would receive methotrexate as a subsequent therapy (see CS Table 47).[1] For the methotrexate treatment arm, it was assumed that patients would receive docetaxel. For the nivolumab treatment arm, it was assumed that patients would receive either docetaxel (50%) or methotrexate (50%). Patients in the UK are not expected to receive either nivolumab or paclitaxel as subsequent systemic therapy. Although in the CheckMate 141 trial, various subsequent therapies were used (see CS Appendix 3), the model restricts the choice of post-discontinuation therapies to docetaxel and methotrexate.[13] The dosing and cost of docetaxel and methotrexate were assumed to be the same as when used as an initial therapy (see CS Section 5.5.2). Furthermore, it was stated that patients in the UK were not expected to receive either nivolumab or paclitaxel as subsequent systemic therapy. Only two patients in CheckMate 141 received subsequent systemic therapy with nivolumab and docetaxel is likely to be preferred over paclitaxel for those patients that would receive a taxane (see CS Section 3.2).

Two scenario analyses were performed. In the first scenario analysis, the proportion of patients receiving subsequent therapy was reduced to 12% in both treatment arms (see CS Scenario 17; Section 5.8.3), based on the market research on the proportion of patients expected to receive later-line therapy for R/M SCCHN.[70] Additionally, the cost of subsequent systemic therapy was excluded from the model (see CS Scenario 18; Section 5.8.3).

Health-state unit costs and resource use

Progression-free and progressed disease

In the CS, unit costs and the frequency of resource use per cycle were assumed to be similar for PF and PD health states. However, the proportion of patients who received each resource use item was varied depending on PF or PD. The type of resource and the proportion of patients who received each resource item were based on the UK study identified in the economic systematic literature review (CS Section 5.5.1).[1] In the absence of specific data regarding frequency per time period, it was assumed for simplicity that each resource item was used once per cycle. In addition, resource use items were only costed in the model if they were received by ≥10% of patients in either the PF or PD state. Table 5.17 depicts disease management costs by health state.

Table 5.17: Disease-management costs by health state

Resource use item	Unit cost	Source	Frequency per cycle & Reference	Progression-free		Progressed disease	
				% patients	Costs per cycle	% patients	Costs per cycle
Dental therapy for radiotherapy effects	£102.71	Total outpatient attendances (450) dental medicines specialties NHS reference cost 2014–15[69]	Frequency: 1 per cycle Reference: Nash-Smyth 2015[71]	22.30%	£22.91	9.80%	£10.07
Depression assessment and management	£73.20	Community Health Services, allied health professionals, A06A1: occupational therapist, adult, one-to-one NHS reference cost 2014–15[69]		12.80%	£9.37	11%	£8.05
Nutritional support	£79.47	Total other currencies, N16AF: specialist nursing, enteral feeding nursing services, adult, face-to-face NHS reference cost 2014–15[69]		58.60%	£46.57	49.40%	£39.26
Pain and symptom management / any supportive care	£78.67	Community Health Services, N21AF: specialist nursing, palliative/respite		53.20%	£41.85	57.90%	£45.55

Resource use item	Unit cost	Source	Frequency per cycle & Reference	Progression-free		Progressed disease	
				% patients	Costs per cycle	% patients	Costs per cycle
		care, adult, face-to-face					
		NHS reference cost 2014–15[69]					
Speech and swallowing therapy	£86.58	Community Health Services, A13A1: speech and language therapist, adult, one-to-one		22.30%	£19.31	9.20%	£7.97
		NHS reference cost 2014–15[69]					
Xerostomia management	£41.16	BNF 2016, pilocarpine (5-10 mg three times per day) as recommended in SIGN 90[72]		24.10%	£9.92	14%	£5.76
Antiemetics	£0.44	eMIT 2015, assumed up to 8 mg per day for 5 days (ondansetron SPC)		59.60%	£0.26	39.60%	£0.17
Management of oral and gastrointestinal mucositis	£6.01	BNF 2016, 15 ml 4 times a day for 7 days (assuming one 300 ml bottle of benzydamine hydrochloride per cycle)		29.60%	£1.78	16.50%	£0.99

Resource use item	Unit cost	Source	Frequency per cycle & Reference	Progression-free		Progressed disease	
				% patients	Costs per cycle	% patients	Costs per cycle
Hematologic growth factor/transfusions (1st unit) (first cycle only)	£170.14	NICE guideline [NG24] Blood Transfusion (2015)[73]		25.90%	£44.07	11.60%	£19.74
Hematologic growth factor/transfusions (subsequent units) (subsequent cycles)	£162.01	NICE guideline [NG24] Blood Transfusion (2015)[73]		25.90%	£41.96	11.60%	£18.79
Total costs per cycle: first cycle				**£196.03**		**£137.56**	
Total costs per cycle: subsequent cycles				**£193.93**		**£136.61**	

BNF = British National Formulary; eMIT = Electronic market information tool; NHS = National Health Service; SIGN = Scottish Intercollegiate Guidelines Network

Disease progression and terminal care costs

In the CS, in addition to the health state costs accrued in PF and PD, the following one-off costs were applied for patients that progressed or died:

i. **Disease progression** – it was assumed that all patients who enter the PD state will have one oncologist visit and one CT scan in order to confirm disease progression
ii. **Terminal care** – it was assumed that patients who enter the death state would incur costs associated with terminal care. This was applied as a single cost which was based on the average cost of community and acute care for patients with cancer in the last eight weeks of their life from research conducted by the King's Fund 2008.[74] The same terminal care cost was applied in the model regardless of prior therapy received.

The costs associated with each event are presented in Table 5.18.

Table 5.18: One-off health state costs associated with disease progression and terminal care

Event	Resource use per event	Unit cost	Total cost	Source
Disease progression			£243.53	NHS reference cost 2014-15[69]
Oncologist visit	1 on entering PD	£131.97		WF01A
CT scan	1 on entering PD	£111.61		RD22Z
Terminal care	1 on entering 'death'	£6,159.66	£6,159.66	NICE ID853[56] and Addicot and Dewar 2008[74]

Source: Based on Table 49 of the CS[1]
CS = company submission; CT = computerised tomography; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD = progressed disease

Adverse event costs

The costs per episode of treating AEs were sourced from currency codes for NHS reference costs and assumptions used in previous appraisals (see Table 5.19).[49, 75] Although CS Table 50 refers to previous technology appraisals (TAs) as source for the cost of different AEs, the full references to the primary sources used in the previous TAs were included in response to the request for clarification question B9.[1, 11] The TAs and primary references used as a source of costs for AEs are presented in Table 5.19.

Table 5.19: Adverse event costs

Adverse Event	Cost	NICE TA Reference	Source
Fatigue	£3,110.11	TA 347 CS and ID811 CS	2014/15 NHS Reference Costs for weighted average of acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC 0-Score 8+ (SA01G-K)
Dyspnoea	£0	ID811 CS	Clinical opinion
Hyponatraemia	£657.84	ID811 CS	Not referenced
Anaemia	£3,110.11	TA 347 CS and ID811 CS	2014/15 NHS Reference Costs for weighted average of acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC 0-Score 8+ (SA01G-K)
Neutropenia	£478.31	T 347 CS and ID811 CS	2014/15 NHS Reference Costs for weighted average of agranulocytosis with CC Score 0-13+ (weighted average)
Dysphagia	£3,305.54	TA 172 ERG report	2006/7 NHS Reference Costs for non-elective inpatient weighted average of Complex major Head, Neck or Ear diagnoses with complications (CZ24O-CZ24P)
Nausea and vomiting	£1,324.62	TA 172 ERG report	2006/7 NHS Reference Costs for non-elective inpatient weighted average of FC05A & FC05B General Abdominal Disorders with complications
Anorexia	£402.57	TA 378 CS	2012/13 NHS Reference costs for weighted average of feeding difficulties and vomiting, with CC Score 0-1+ (PA28A-B)

Source: Based on Table 44 of the response to the request for clarification[11]
CS = company submission; ERG = Evidence Review Group; NHS = National Health Service; TA = technology appraisal

ERG comment: In response to clarification question B8, the company indicated that the proportion of patients receiving subsequent systemic therapy was based on data from CheckMate 141.[11] These proportions were similar between treatment arms (nivolumab, [redacted] and IC, [redacted]).[3] It was unclear to the ERG why these proportions were assumed to be treatment dependent and hence in the ERG base-case an average of the proportions of subsequent therapies from the Checkmate 141 trial was used. The ERG preferred not to use the 12% provided by the company in a scenario analysis as the methods and setting used to obtain this proportion were unclear. However, the variety of experimental drugs that were used as subsequent therapies in CheckMate 141 and costs for these drugs are not likely to be available. Hence, the cost of subsequent systemic therapy is likely to be underestimated. Moreover, the duration of subsequent therapy used in the analysis was 1.9 months based on the median observed duration of IC treatment. However, CS Table 55 shows the mean duration of subsequent therapy based on the economic model so the preferred assumption would be to use this duration in the calculations. Although the mean duration of subsequent therapy is higher, the incremental difference between nivolumab and IC, in terms of subsequent therapy, is not likely to have an impact on the results.

The ERG has amended the dose of docetaxel using 75 mg/m^2 Q3W in the base-case presented in Section 5.3. Moreover, in an exploratory analysis, the ERG used an adjusted dosage for nivolumab (fixed dose of 240 mg) that was recommended on 13 September 2016, by the FDA for all approved (monotherapy) indications in lung cancer, melanoma and renal-cell carcinoma.[76]

5.2.10 Cost effectiveness results

Nivolumab was more effective than docetaxel, methotrexate and paclitaxel in terms of both QALYs and LYs. It should be noted that the QALYs and LYs for docetaxel, methotrexate and paclitaxel were equal (due to the assumption of equivalence) and were estimated based on the IC arm. The main source of QALY and LY benefit associated with nivolumab treatment came from an extension in the period of time spent in the PD state (Table 5.20). This substantial QALY gain in the PD state with nivolumab is reflective of the improved OS for nivolumab versus IC (with relatively similar PFS), and the higher utility associated with nivolumab treatment in the PD state.

Table 5.20: QALY and LY by health state

Health state				
	Nivolumab QALYs	**IC QALYs[a]**	**Incremental QALYs**	**% of total increment**
PF	[redacted]	0.18	[redacted]	15%
PD	[redacted]	0.22	[redacted]	83%
AE disutility	[redacted]	-0.03	[redacted]	2%
Total	[redacted]	0.37	[redacted]	100%
	Nivolumab LYs	**IC LYs[a]**	**Incremental LYs**	**% of total increment**
PF	0.34	0.26	0.09	13%
PD	0.99	0.39	0.60	87%
Total	1.33	0.65	0.68	100%

Source: Based on Table 56 of the CS[1] and response to request for clarification question B12[11]
Note: [a] QALYs and LYs were equal for docetaxel, methotrexate and paclitaxel
AE = adverse event; CS = company submission; IC = investigator's choice; LY, life year; PD = progressive disease; PF = progression-free; QALY = quality-adjusted life year

Nivolumab was also associated with higher life time costs than docetaxel, methotrexate and paclitaxel irrespective of whether the PAS for nivolumab was applied. It should be noted that the costs for docetaxel, methotrexate and paclitaxel only differed with regards to the costs of drug acquisition and subsequent therapy (other costs were equal for these comparators, see Section 5.2.9). The overall differences in cost between nivolumab with PAS and the comparators were largely (87%) due to higher drug acquisition costs for nivolumab (Table 5.21).

Table 5.21: Costs by health state (nivolumab with PAS)

Item	Nivolumab cost	Docetaxel cost	Paclitaxel cost	Methotrexate cost	Incremental costs[a]	Absolute increment[a]	% of total increment
PF disease management	[redacted]	£655	£655	£655	[redacted]	[redacted]	1%
PD disease management[b]	[redacted]	£6,805	£6,805	£6,805	[redacted]	[redacted]	5%
Disease progression (one-off cost)	[redacted]	£239	£239	£239	[redacted]	[redacted]	0%
Drug acquisition	[redacted]	£170	£234	£166	[redacted]	[redacted]	87%
Drug administration	[redacted]	£2,522	£2,522	£2,522	[redacted]	[redacted]	3%
Monitoring	[redacted]	£876	£876	£876	[redacted]	[redacted]	3% - 4%
Subsequent treatment	[redacted]	£621	£621	£621	[redacted]	[redacted]	0%
Adverse events	[redacted]	£651	£651	£651	[redacted]	[redacted]	1%
Total	[redacted]	**£12,538**	**£12,603**	**£12,535**	[redacted]	[redacted]	**100%**

Source: Based on Tables 60-62 of the CS[1]

Notes: [a] Increment for nivolumab versus comparators; [b] The one-off cost of terminal care was included in PD disease management costs

CS = company submission; PAS = Patient Access Scheme; PD = progressed disease; PF = progression free

In the company's base-case analysis, the increased QALYs and costs for nivolumab resulted in ICERs of £34,902, £34,777 and £34,908 versus docetaxel, paclitaxel and methotrexate, respectively (Table 5.22).

Table 5.22: Deterministic company base-case results (nivolumab with PAS)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	£12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	£12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	£12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908

Source: Based on Table 54 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LY = life-years; PAS = Patient Access Scheme; QALYs = quality-adjusted life years

5.2.11 Sensitivity analyses

The company presented probabilistic sensitivity analysis (PSA), deterministic sensitivity analysis (DSA) and deterministic scenario analysis.

Probabilistic sensitivity analysis

The base-case results using PSA (1,000 simulations) are presented in Table 5.23 and resulted in slightly higher ICERs than those presented for the deterministic company base-case. The ICERs were £35,157, £35,025 and £35,091 for nivolumab versus docetaxel, paclitaxel and methotrexate, respectively.

Table 5.23: Probabilistic company base-case results (nivolumab with PAS)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Nivolumab	[redacted]	[redacted]			
Docetaxel	£12,544	0.37	[redacted]	[redacted]	£35,157
Paclitaxel	£12,613	0.37	[redacted]	[redacted]	£35,025
Methotrexate	£12,576	0.37	[redacted]	[redacted]	£35,091

Source: Based on Table 54 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; PAS = Patient Access Scheme; QALYs = quality-adjusted life years

The company provided incremental cost effectiveness planes and cost effectiveness acceptability curves (CEACs; CS Figures 42-53) using pairwise comparisons of nivolumab versus the comparators (instead of comparing all comparators simultaneously). Based on these pairwise comparisons, the company reported a 70% probability of nivolumab (with PAS) being cost effective at a threshold of £50,000 per QALY.

Deterministic sensitivity analysis

The company conducted DSA by varying all parameters for which there were single input values into the model by ±15% of their mean value in order to identify key model drivers. The company acknowledged that the parametric distributions chosen to model treatment effectiveness (i.e. OS, PFS and TTD) were not captured in the deterministic sensitivity analysis.

The DSA results are presented using tornado diagrams with the top 10 drivers of cost effectiveness in CS Figures 54-59. The company identified the following parameters as the main of cost effectiveness (in order of importance):

1. Nivolumab utility for PD
2. Nivolumab treatment frequency
3. Nivolumab treatment dose
4. Average weight
5. Nivolumab cost per vial (100 mg pack)
6. Nivolumab utility for PFS
7. Comparator utility PD
8. Comparator utility PFS
9. Nivolumab cost per vial (40 mg pack)
10. Comparator treatment frequency

Deterministic scenario analysis

The company performed various deterministic scenario analyses, see Table 5.24.

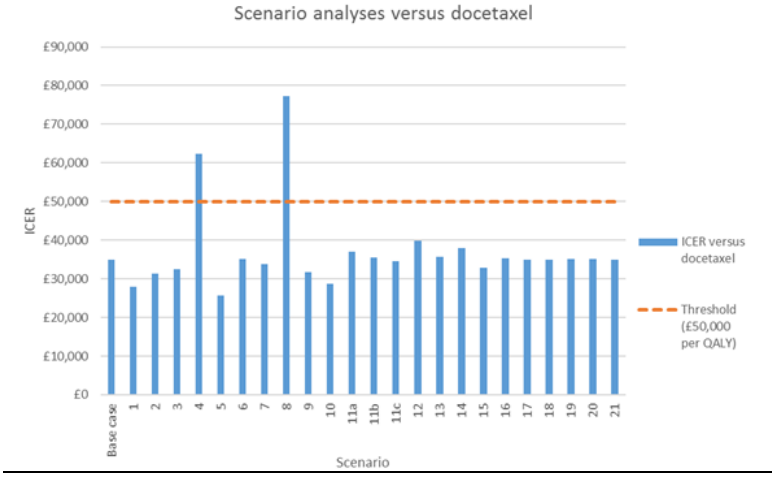
Table 5.24: Deterministic scenario analyses performed by the company

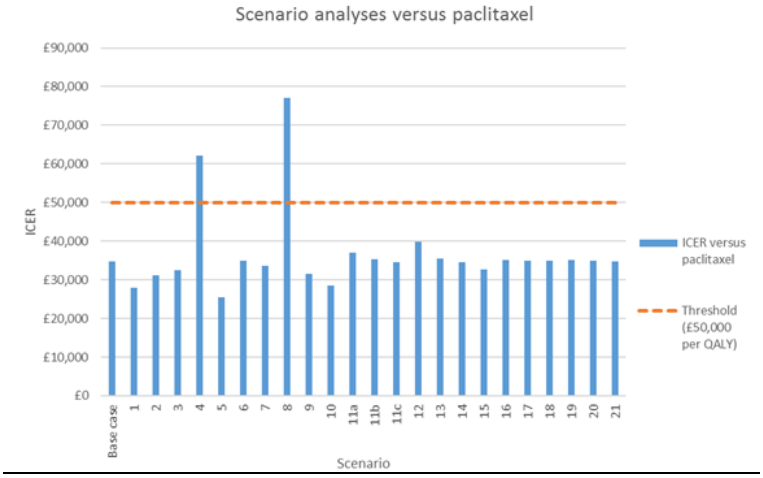
Scenario	Description	Signpost CS
1-3	Alternative clinical stopping rules imposed at 1, 2 and 3 years	Tables 65 and 66
4-9	Alternative parametric survival distributions for OS, PFS and TTD	Tables 67-72
10	Using PFS to model time on treatment rather than TTD; assuming no treatment beyond progression	Tables 73 and 74
11a–c	Alternative time horizons of a) 10 years, b) 15 years and c) 25 years	Tables 75 and 76
12	Using treatment independent health-state utilities	Tables 77 and 78
13	Using no disutility for AEs	Tables 77 and 78
14	Using Docetaxel 75 mg/m^2 Q3W dose for treatment costs	Tables 77 and 78
15	Permitting vial sharing; i.e. assuming no drug wastage	Tables 77 and 78
16	Using 100% dose intensity; i.e. assuming no dose delay	Tables 77 and 78
17	Using a reduced % of patients receiving subsequent systemic therapy; reduced by 12% based on market research	Tables 77 and 78
18	Using no subsequent systemic therapy costs	Tables 77 and 78
19	Using no terminal care cost	Tables 77 and 78
20	Using average weight and BSA from the overall trial population	Tables 77 and 78
21	Using average BSA from UK[68] cancer patients	Tables 77 and 78

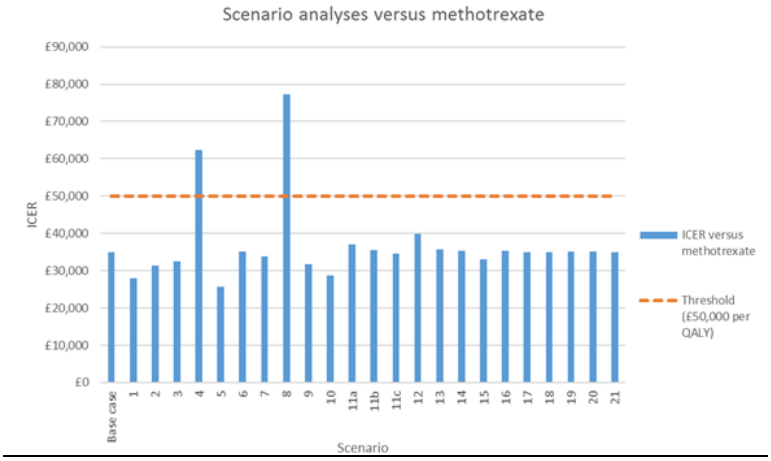
AE = adverse event; BSA = body surface area; CS = company submission; OS = overall survival; PFS = progression-free survival; Q3W = once every 3 weeks; TTD =progression-free survival; UK = United Kingdom

The results of the scenario analyses are summarised in Figure 5.7, showing that scenario 4, 8 and 12 were the most influential scenarios (in terms of increase in ICER) when considering nivolumab with PAS. These scenarios considered alternative distributions to estimate OS (scenario 4, using Weibull distribution for OS; ICER increased to £62,156 - £62,399 and TTD (scenario 8, using 2-spline odds distribution for TTD; ICER increased to £77,111 - £77,232) and using treatment independent health-state utilities (scenario 12; ICER increased to £39,767 - £39,917). Moreover, scenario 14 showed that when using docetaxel 75 mg/m^2 Q3W dose (which is the more routinely-used dose in the UK) to calculate docetaxel treatment costs, instead of the docetaxel dosing as used in the CheckMate 141 trial, the ICER would increase by £2,800 to £37,978 for nivolumab (with PAS) versus docetaxel.

Figure 5.7: Scenario analyses presented in the CS considering nivolumab with PAS







Source: Based on Figures 60-62 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year

ERG comment: Given that PFS was similar between nivolumab and IC while nivolumab resulted in a clinically relevant median OS benefit, a post-progression benefit of nivolumab is to be expected. However, it is noteworthy that in the CS base-case the majority (83%) of the estimated QALY gain (87% of the estimated LY gain) is attributable to the period after disease progression has been

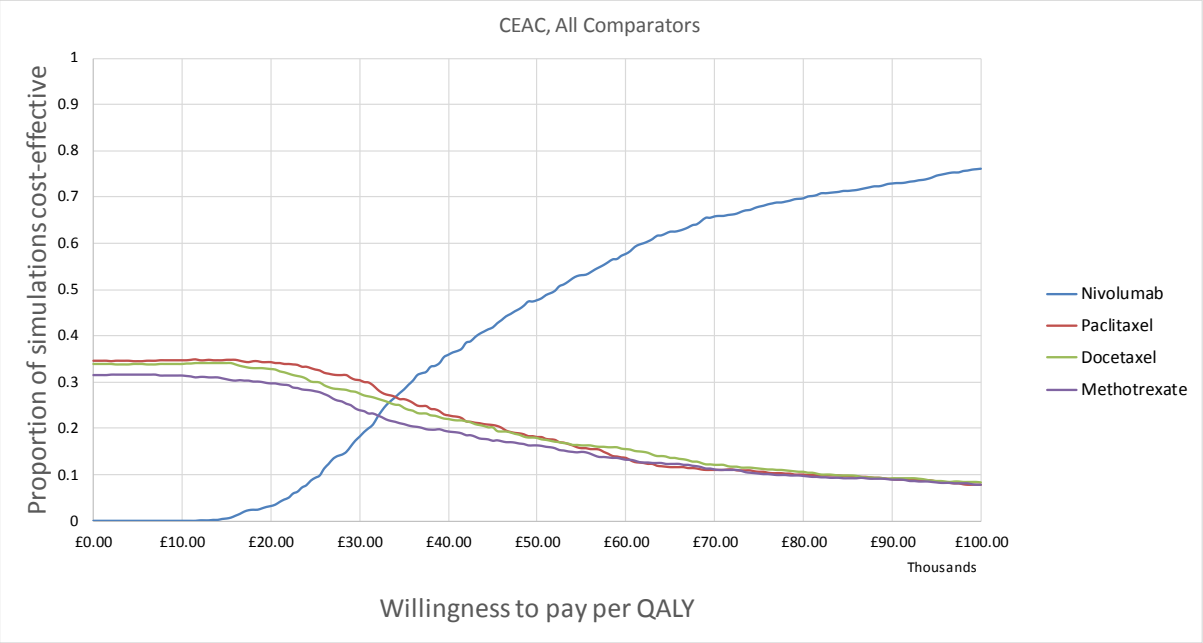
confirmed. Moreover, 78% of the estimated LY gain is attributable to the period after treatment discontinuation. This implies that additional benefit continues to accrue to patients whose disease has progressed and/or to patients who no longer receive nivolumab. This was also observed in the assessment of nivolumab for lung cancer (non-small-cell, squamous, metastatic; ID811[49]). Moreover, in the appraisal consultation document of this assessment (issued October 2016), the committee concluded that *"the CheckMate-017 trial did not provide evidence for a dramatic gain in survival after disease progression with nivolumab compared with docetaxel"* and that *"some gain in survival after disease progression would be plausible and would be consistent with the mechanism of action of nivolumab; however, it concluded overall that the size of the gain implied by the company's model was neither plausible nor supported by the clinical-trial evidence"*.[77] However, it is unclear whether these statements based on the CheckMate 017 trial are also applicable to the present assessment, based on the CheckMate 141 trial. Given these uncertainties with regards to the post-progression benefits of nivolumab (i.e. long-term extrapolation), the ERG performed exploratory analyses using a shorter time horizon.

It should be noted that both the DSA and PSA performed by the company did not consider the uncertainty in the estimation of the OS, PFS and TTD (i.e. parameters for the time-to-event models were considered fixed). Therefore, the incremental cost effectiveness planes, reported in the CS, were not presented in the ERG report as the uncertainty presented in these plots is very likely to be underestimated. Moreover, the CEACs presented in the CS were not presented in the ERG report as these were three pairwise comparisons instead of all treatments simultaneously. The latter approach would be considered good practice by the ERG and was therefore requested (clarification question B13). The updated CEACs provided by the company considered all treatments simultaneously, incorporated treatment effectiveness parameters stochastically (though the correlation between the parameters was not incorporated) and showed that with the PAS, the probability that nivolumab is cost effective is [redacted] and [redacted] at thresholds of £30,000 and £50,000 per QALY respectively (Figure 5.8).[11]

The scenario analyses, provided by the company using treatment specific effectiveness parameters for OS, PFS and TTD resulted in similar ICERs compared with the company base-case and ranged from £33,756 to £34,286 for nivolumab with PAS (clarification in response to request for clarification, Table 22).[11]

In the ERG base-case (Section 5.3), the estimation of OS, PFS and TTD will be incorporated stochastically (as in the updated company base-case). Moreover, the standard deviation for utility values was incorrectly used in the PSA by the company; this will be corrected in the ERG base-case (using the standard error).

Figure 5.8: Cost effectiveness acceptability curves (nivolumab with PAS)



Source: economic model provided by the company in response to the request for clarification[11]
PAS = Patient Access Scheme; QALY = quality-adjusted life year

5.2.12 Model validation and face validity check

The company indicated that there were no data sources against which the model could be externally validated. Although registry databases (Surveillance, Epidemiology, and End Results Program (SEER)[78, 79] and UK Oxford Cancer Intelligence Unit (OCIU)[80]) were considered as potential data sources for validation of long-term extrapolations, these data sources were not used. Instead, clinical trials conducted in advanced squamous NSCLC population and clinical expert opinion were sought to validate survival outcomes and inputs included in the model.

In the CS, the following were considered to seek validation of survival outcomes by clinical experts:

1) expected OS with comparator therapies used in current clinical practice
2) expected mean PFS and TTD
3) relationship between OS, PFS and TTD under selected distribution for:
    a) illogical inconsistencies of the distributions (i.e. OS falling below PFS or TTD)
    b) plausibility of predicted mean PFS and TTD
    c) clinical (im-)plausibility for probability of death for R/M SCCHN patients receiving either nivolumab or IC versus those of the general age-matched population.

In the CS, it was stated that clinical experts were asked to validate the following model inputs:

1) Relevant adverse events and their associated disutility estimates
2) Disease management resource use for SCCHN
3) Equivalence of efficacy between comparators
4) Equivalence of efficacy of docetaxel when used at the trial dosing frequency and at clinical practice dosing frequency

A comparison of clinical outcomes (PFS, TTD and OS) predicted by the base-case analysis and CheckMate 141 is presented in CS Table 55 and reproduced in Table 5.25.[1] The company indicated that compared to median OS, PFS and TTD from CheckMate 141, the model over-predicted median PFS and median TTD and under-predicted median OS for nivolumab (versus the nivolumab trial arm),

whereas for the comparators, the model provided very close estimates for median PFS and median OS and slightly over-predicted median TTD (versus the IC trial arm).

The base-case choice of distribution for OS (lognormal), PFS (generalised-gamma) and TTD (log logistic) was considered valid based on the longer term data from the advanced squamous NSCLC population (for nivolumab) and expert clinical opinion (for comparator therapies). Predicted OS with nivolumab or IC did not fall below the PFS or TTD curves at any point over the 20 year time horizon. Mean TTD ([redacted]) and mean PFS (4.6 months) on nivolumab had a clinically plausible relationship [redacted]. The predicted mean TTD and the relative lengths of PFS and TTD were aligned to expert clinical opinion.

Table 5.25: Model predictors of clinical outcomes compared with CheckMate 141

Outcome, months (95% CI)	Nivolumab		Comparators*	
	CheckMate 141	Economic model	CheckMate 141	Economic model
PFS				
Median	2.0 (1.9, 2.1)	2.6	2.3 (1.9, 3.1)	2.6
Mean	-	4.6	-	3.6
TTD				
Median	1.9 (1.6, 2.3)	3.0	1.9 (1.6, 2.0)	2.3
Mean	-	[redacted]	-	3.6
OS				
Median	7.5 (5.5, 9.1)	7.1	5.1 (4.0, 6.0)	5.0
Mean	-	17.7	-	8.4

Source: Based on Table 55 of the CS[1]

Gillison 2016[27] and CheckMate 141 CSR (7th June 2016)[25] for OS and TTD; Ferris 2016[26] and CheckMate 141 CSR (7th June 2016)[25] for PFS

Note: * Based on the total IC arm of CheckMate 141

CI = confidence interval; CS = company submission; IC = investigator's choice; OS = overall survival; PFS = progression-free survival; TTD = time to discontinuation.

ERG comment: The face validity of the survival outcomes and model inputs were performed by clinical experts as indicated in the CS. The ERG also performed a face validation of the model outcomes. The ERG observed that predicted PFS and TTD curves were not plausible for IC as these curves were crossing (see Section 5.2.6). In the CS, no information was provided regarding verification/internal validity. It was not mentioned whether an assessment of the technical validity of the model (by a modelling expert) was undertaken (to test accuracy of the programming and the extraction of data inputs). However, the ERG undertook a systematic approach to check large parts of the model and no major errors were detected. The company mentioned that external validation was not possible. Also, cross validation was not possible as no other models were identified for this indication. The ERG believes that the lack of external validation hampers the interpretation of the CS, particularly given the lack of evidence to support the long-term post-progression benefits of nivolumab.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations from Section 5.2, the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the CS. Some of the adjustments considered in Section 5.2 were already incorporated in the model file provided by the company in response to clarification, which provided an updated CS base-case.[11] Therefore, the ERG will use the updated CS base-case as a starting point for its analysis. These adjustments made by the ERG/provided in the updated company base-case form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[81]):

- Fixing errors (correcting the model were the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred)

Additionally, one exploratory sensitivity analysis and one threshold analysis (see Section 5.3.2) were performed by the ERG to examine the potential impact of alternative assumptions on the cost effectiveness estimates.

Fixing errors

1. Fixing errors consisted of:
    a. Adding OS, PFS and TTD as probabilistic parameters in the PSA (without incorporating the correlation between parameters)
    This is incorporated in the updated company base-case. It is in line with good modelling practice to include all empirically measured parameters as stochastic (based on the empiric variation) in the PSA.

    b. Incorporate NHS reference costs in PSA using upper and lower quartiles
    This is incorporated in the updated company base-case. It is in line with good modelling practice to include all empirically measured parameters as stochastic (based on the empiric variation) in the PSA.

    c. Changing the standard deviation into standard error for utility scores in the PSA
    The standard deviation was incorrectly labelled/incorporated as standard error in the economic model.

    d. Using all available baseline utility data
    The ERG used utility estimates based on all patients with a baseline measurement (i.e. utility data from Table 29 of the clarification response).

Fixing violations

2. Adding adverse event costs (£418.91) and disutility (-0.15) for pneumonitis
    The ERG considered pneumonitis a potentially relevant AE and was therefore included in the ERG base-case (see section 5.2.6 for more details).

3. Using docetaxel dosing conform UK clinical practice
    The ERG altered the dosing of docetaxel to once every three weeks, 75 mg/m^2 in accordance with UK clinical practice and because there is no evidence to support a difference in efficacy between the two docetaxel schemes (see Sections 5.2.4 and 5.2.9 for more details).

Matters of judgment

4. Using the generalised-gamma distribution for TTD
   The ERG believes the generalised-gamma distribution is more appropriate for TTD (see Section 5.2.6 for more details)

5. Using treatment independent utility
   Given the uncertainty in the estimation of the treatment dependent utility scores, the ERG judges it to be most appropriate to use treatment independent utility scores (see Section 5.2.8 for more details).

6. Using treatment independent proportions for subsequent treatments
   The ERG judges it to be more plausible to use treatment independent proportions for subsequent treatments (see Section 5.2.9 for more details).

5.3.1 Probabilistic sensitivity analysis (ERG base-case)

The ERG performed a PSA to obtain the ERG base-case incorporating all abovementioned adjustments. This resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate respectively (Table 5.26).

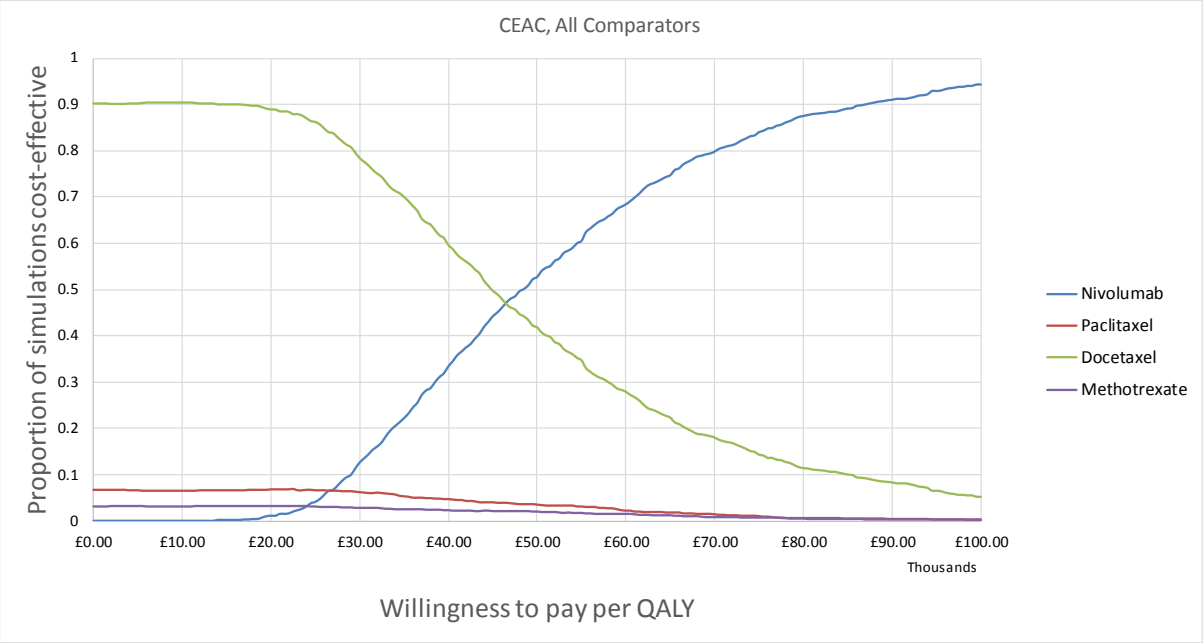
Table 5.26: ERG-base-case (probabilistic)

	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
ERG base-case	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£10,276	0.41	[redacted]	[redacted]	£49,848
	Paclitaxel	£11,732	0.41	[redacted]	[redacted]	£46,611
	Methotrexate	£11,753	0.41	[redacted]	[redacted]	£46,565

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

The CEACs based on the ERG base-case (Figure 5.9) showed that nivolumab has a probability of being cost-effective of 13% and 53% at thresholds of £30,000 and £50,000 per QALY gained, respectively.

Figure 5.9: Cost effectiveness acceptability curves (nivolumab with PAS, ERG base-case)



CEAC = cost effectiveness acceptability curve; PAS = Patient Access Scheme; QALY = quality-adjusted life year

5.3.2 Additional exploratory and threshold analyses performed based on the ERG base-case

One additional exploratory sensitivity analysis and one threshold analysis were performed by the ERG to examine the potential impact of alternative assumptions on the cost effectiveness estimates. These analyses were performed on the ERG base-case and investigated the impact of the following adjustments:

7. Assumption of nivolumab fixed dose of 240 mg every two weeks (independent of weight)
   The FDA modified the approved recommended dosage regimen for nivolumab for the currently approved indications for renal cell carcinoma, metastatic melanoma, and non-small cell lung cancer into 240 mg every two weeks. Although this is currently not applicable to the present population, the impact of this dosage modification is explored.
8. Assumption of equivalence between docetaxel and paclitaxel
   The equivalence assumption between paclitaxel and docetaxel can be questioned (Section 4.3). Therefore, it is examined how much more effective paclitaxel would need to be (compared with docetaxel) in order to be cost effective compared with nivolumab.
9. Limiting extrapolation of treatment benefits by using shorter time horizons (two and five year)
   It is noteworthy that in the CS base-case the majority (83%) of the estimated QALY gain (87% of the estimated LY gain) is attributable to the period after disease progression has been confirmed (Sections 5.2.10 and 5.2.11). The lack of external validation of long-term outcomes hampers the interpretation of this extrapolation. Therefore, different time horizons are explored (in addition to the time horizons explored by the company in CS scenario analysis 11)

The exploratory analysis, using an adjusted dosage for nivolumab, resulted in slightly increased ICERs versus nivolumab (with PAS) of £50,160 to £53,439 (Table 6.2). The threshold analyses considering the assumption of equivalence between docetaxel and paclitaxel, indicated that for paclitaxel to be cost effective compared with nivolumab (at a threshold of £50,000 per QALY), the HR for paclitaxel versus docetaxel should be no higher than approximately 0.93 (for both OS and PFS). The shorter time

horizons resulted in increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year).

5.4 Conclusions of the cost effectiveness section

The majority of the cost effectiveness searches in the CS were well documented and easily reproducible, and were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[16] The ERG expressed concerns on the lack of relevant MeSH indexing terms on Embase.com, the restriction to English language only, and the omission of specific searches for the identification of measurement and valuation of health effects data.

Reviewing the overall evidence, the ERG confirmed that there was no existing cost effectiveness model for nivolumab for the current indication, and thus that development of a de novo model was necessary. The economic model described in the CS is considered by the ERG to meet the NICE reference case. The company model follows a logical structure with respect to the nature of the disease. The economic model was primarily informed by the CheckMate 141 trial. The IC arm from the CheckMate 141 trial (mixture of treatment with docetaxel, methotrexate and cetuximab) was used to inform treatment effectiveness for docetaxel, paclitaxel and methotrexate. This was based on the assumption of equivalence in terms of treatment effectiveness between docetaxel and methotrexate as well as between docetaxel and paclitaxel.

The company base-case ICERs (probabilistic) of nivolumab (with PAS) compared with docetaxel, paclitaxel and methotrexate were £35,157, £35,025 and £35,091 respectively. The cost effectiveness results were generally robust under most of the scenario and one-way sensitivity analyses conducted by the company. However, in two scenario analyses considering either alternative distributions for OS or alternative distributions for TTD, the ICERs of nivolumab (with PAS) versus the comparators increased to £62,156 to £62,399 and £77,111 to £77,232 respectively. Also, when examining the nivolumab utility value for progressed disease in a sensitivity analysis, the ICER increased by almost £18,000. It should be noted though that, in the original CS, the parameters of the distributions estimating OS, PFS and TTD were not considered in the sensitivity analyses and that the one-way sensitivity analyses were often based on arbitrary estimates of the variance (i.e. using ±15% of the mean value) even if empirical estimates are available (e.g. using upper and lower quartiles for the NHS reference costs).

The ERG has incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate respectively. The most influential adjustments/corrections made by the ERG were 1) using a generalised-gamma distribution for estimating TTD; 2) using treatment independent utilities for PFS and PD health state utility values and; 3) using a dose and frequency of administration for docetaxel (75 mg/m^2 Q3W) consistent with UK clinical practice. Moreover, in an exploratory analysis, the ERG used an adjusted dosage for nivolumab (fixed dose of 240 mg every two weeks) that was recently recommended by the FDA for renal-cell carcinoma, metastatic melanoma, and non-small cell lung cancer. This exploratory analysis, which was performed conditional upon the ERG base-case, resulted in ICERs (with PAS) of £50,160 to £53,439. Moreover, applying shorter time horizons to explore the impact of the extrapolating estimated benefits of costs resulted in increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year).

The equivalence assumptions between docetaxel and methotrexate as well as between docetaxel and paclitaxel can be questioned. Moreover, a scenario analysis, provided by the company (response to request for clarification letter Table 22),[11] using treatment specific effectiveness estimates for docetaxel and methotrexate (instead of using IC effectiveness), showed that the assumption of equivalence between docetaxel and methotrexate is not likely to be influential in terms of incremental QALYs,

incremental costs and the ICER. To examine the assumption of equivalence between docetaxel and paclitaxel, the ERG performed a threshold analysis (conditional on the deterministic ERG base-case). This analysis indicated that if paclitaxel is more effective than docetaxel in terms of OS and PFS, up to a HR of approximately 0.93, nivolumab would not be cost effective compared with paclitaxel (assuming a threshold of £50,000 per QALY). Additionally, the cost effectiveness of nivolumab versus paclitaxel is uncertain given that, in Section 4.4, it is concluded there is some evidence, albeit weak, that paclitaxel is possibly more effective than nivolumab.

An additional area of uncertainty is the generalisability of the CheckMate 141 trial to UK clinical practice. This is questioned in Section 4 of this report, most particularly in terms of patient characteristics that would determine both intended treatment and prognosis. Section 4 concludes that despite that it seems plausible that nivolumab extends life expectancy, it is unclear by how much in comparison to docetaxel, paclitaxel and methotrexate. As the treatment effectiveness in the health economic model is primarily based on the CheckMate 141 trial, these reservations are also applicable to the estimated cost effectiveness, in particularly considering the magnitude of the post-progression benefits.

In conclusion, given the ERG base-case ICERs are estimated to be around £50,000 per QALY gained, the large uncertainty regarding extrapolation and post-progression benefits in combination with the lack of external validation of long-term outcomes and the doubt about the generalisability of the CheckMate 141 trial results to the UK the decision, uncertainty around the cost effectiveness of nivolumab remains substantial.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 shows how each individual change impacts the ICER plus the combined effect of all changes simultaneously. The analyses numbers in Table 6.1 correspond to the analyses numbers reported in Section 5.3. Also, the exploratory analysis is presented in Table 6.2 (conditional on the ERG base-case). Finally, the threshold analyses are discussed in Section 5.3.2. Appendix 2 contains technical details on the analyses performed by the ERG.

Table 6.1: ERG base-case (probabilistic), nivolumab with PAS

	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
Company base-case (original)	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£12,544	0.37	[redacted]	[redacted]	£35,157
	Paclitaxel	£12,613	0.37	[redacted]	[redacted]	£35,025
	Methotrexate	£12,576	0.37	[redacted]	[redacted]	£35,091
Company base-case (post-clarification)	Nivolumab	[redacted]	[redacted]			
	Docetaxel	12,569	0.37	[redacted]	[redacted]	£34,914
	Paclitaxel	12,710	0.37	[redacted]	[redacted]	£34,807
	Methotrexate	12,626	0.37	[redacted]	[redacted]	£34,644
1) Fixing errors	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£12,596	0.37	[redacted]	[redacted]	£34,690
	Paclitaxel	£12,618	0.37	[redacted]	[redacted]	£34,643
	Methotrexate	£12,534	0.37	[redacted]	[redacted]	£34,812
2) Adding pneumonitis[a]	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£12,579	0.37	[redacted]	[redacted]	£35,557
	Paclitaxel	£12,680	0.37	[redacted]	[redacted]	£35,358
	Methotrexate	£12,587	0.37	[redacted]	[redacted]	£35,532
3) Docetaxel dose conform UK practice[a]	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£10,775	0.37	[redacted]	[redacted]	£37,987
	Paclitaxel	£12,593	0.37	[redacted]	[redacted]	£34,455
	Methotrexate	£12,221	0.37	[redacted]	[redacted]	£35,181
4) Using the generalised-gamma distribution for TTD[a]	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£12,253	0.37	[redacted]	[redacted]	£41,081
	Paclitaxel	£11,667	0.37	[redacted]	[redacted]	£42,231
	Methotrexate	£12,220	0.37	[redacted]	[redacted]	£41,166
5) Using treatment	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£12,644	0.41	[redacted]	[redacted]	£39,708
	Paclitaxel	£12,071	0.41	[redacted]	[redacted]	£40,999

	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
independent utility scores[a]	Methotrexate	£12,627	0.41	[redacted]	[redacted]	£39,748
6) Using treatment independent % subsequent therapies[a]	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£12,096	0.37	[redacted]	[redacted]	£35,035
	Paclitaxel	£12,054	0.37	[redacted]	[redacted]	£35,111
	Methotrexate	£12,088	0.37	[redacted]	[redacted]	£35,044
ERG base-case (combining adjustments 1-6)	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£10,276	0.41	[redacted]	[redacted]	£49,848
	Paclitaxel	£11,732	0.41	[redacted]	[redacted]	£46,611
	Methotrexate	£11,753	0.41	[redacted]	[redacted]	£46,565

Note: [a] This scenario is conditional on the fixing errors adjustment (adjustment 1)
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

Table 6.2: Exploratory analyses; nivolumab with PAS

	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
Company base-case (post-clarification)	Nivolumab	[redacted]	[redacted]			
	Docetaxel	12,569	0.37	[redacted]	[redacted]	£34,914
	Paclitaxel	12,710	0.37	[redacted]	[redacted]	£34,807
	Methotrexate	12,626	0.37	[redacted]	[redacted]	£34,644
ERG base-case	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£10,276	0.41	[redacted]	[redacted]	£49,848
	Paclitaxel	£11,732	0.41	[redacted]	[redacted]	£46,611
	Methotrexate	£11,753	0.41	[redacted]	[redacted]	£46,565
ERG base-case using fixed dose of nivolumab (240 mg)	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£10,316	0.41	[redacted]	[redacted]	£53,439
	Paclitaxel	£11,675	0.41	[redacted]	[redacted]	£50,432
	Methotrexate	£11,792	0.41	[redacted]	[redacted]	£50,160
ERG base-case using time horizon of 2-year	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£10,257	0.37	[redacted]	[redacted]	£98,925
	Paclitaxel	£11,517	0.37	[redacted]	[redacted]	£91,867
	Methotrexate	£11,374	0.37	[redacted]	[redacted]	£92,649
ERG base-case using time horizon of 5-year	Nivolumab	[redacted]	[redacted]			
	Docetaxel	£10,593	0.40	[redacted]	[redacted]	£63,833
	Paclitaxel	£11,708	0.40	[redacted]	[redacted]	£60,414
	Methotrexate	£11,846	0.40	[redacted]	[redacted]	£59,984

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

7. END OF LIFE

The NICE end of life criteria state that *"the treatment is indicated for patients with a short life expectancy, normally less than 24 months and there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment".*[82]

According to the CS, *"the clinical evidence presented from CheckMate 141 supports the consideration of nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy as a 'life-extending medicine at the end of life,' in accordance with the revised NICE end-of-life criteria.[82]"*[1]

The CS presents the data available for the two criteria in a table, reproduced below as Table 7.1. The supporting text in the CS includes further information on both criteria, notably for the second criterion.

"At the interim analysis of CheckMate 141, median OS was extended by 2.43 months in the nivolumab arm (7.5 months [95% CI, 5.5, 9.1]) versus the IC arm (5.1 months [95% CI, 4.0, 6.0]).[27] This extension in life is just below the 3 months that are normally required of therapies to meet the NICE end-of-life criteria, however, the following points should be considered:

1. *For patients with platinum-refractory R/M SCCHN, this extension to life represents a considerable survival benefit (1.47-fold greater median OS with nivolumab) compared to that achieved with IC of therapy alone*
2. *The improvement in OS observed with nivolumab was considered to be statistically significant, with nivolumab associated with a significant 30% reduction in the risk of death compared to IC of therapy (HR, 0.70 [97.73% CI, 0.51, 0.96]; p-value = 0.0101)[27]*
3. *Importantly, if the long-term survival benefits of nivolumab seen in other cancer indications are replicated in R/M SCCHN, the survival benefit for nivolumab versus IC, in terms of mean OS, is likely to increase. The median value for OS does not necessarily represent the durable survival benefit that could potentially be achieved by some patients[83]*
4. *The mean OS benefit with nivolumab was estimated to be greater than 3 months compared to the IC arm using extrapolated data from CheckMate 141 in the economic model (see Table 27 in Section 5.3.2* [of the CS]*), regardless of the parametric survival distribution used*

Based on mean OS predicted by the economic model, nivolumab is expected to provide an extension in life that is greater than the 3 months cited in the NICE end-of-life criteria [Table 7.1]. *Notably, both end-of-life criteria were met using any of the parametric survival distributions that were explored for the economic analysis (see Table 27 in Section 5.3.2* [of the CS]*)".*

Table 7.1: End of life criteria

Criterion	Data available
The treatment is indicated for patients with a short life-expectancy, *normally* less than 24 months	Mean OS predicted in the base-case of the cost-effectiveness analysis was 8.4 months for IC. A mean OS of less than 24 months for the IC arm was predicted for all parametric survival distributions that were explored.
There is sufficient evidence to indicate that the treatment offers an extension to life, *normally* of at least an additional 3 months, compared with current NHS treatment	Mean OS predicted in the base-case of the cost-effectiveness analysis was 17.7 months for nivolumab, representing an extension in mean OS of 9.3 months relative to IC of therapy. An extension in OS of more than 3 months was predicted for each parametric survival distribution that was explored.
Source: Based on Table 22 of the CS[1] CS = company submission; IC = investigator's choice; OS = overall survival	

ERG comment: The ERG believes that the first criterion (life expectancy of less than 24 months) has been met. As detailed in Table 4.6, median overall survival for all treatments (nivolumab and IC as well as treatments used in the IC arm) is clearly below the 24 months threshold defined by NICE.[82]

On the second criterion (extension of life of at least three months), the ERG agrees with the company who highlighted *"this extension in life is just below the 3 months that are normally required of therapies to meet the NICE end-of-life criteria"*. In regards to the points raised by company (see above), the ERG notes that:

- There is considerable uncertainty regarding the results of CheckMate 141 concerning
  - The quality of the trial (Sections 4.1.4 and 4.2.1),
  - The generalisability of the results (gender differences, differences between EU and North America and treatment given; discussed in Section 4.2.1)
- One of the comparators defined in the final scope (paclitaxel) has not been included (discussed in Section 4.3) while the IC is hard to interpret and includes one comparator not defined in the scope (cetuximab; see Section 3.3)
- In particular, if most patients are like those for whom methotrexate would be prescribed then the gain in median OS could be as much as three months (See Table 4.6). However, the percentage of participants chosen by clinicians to receive methotrexate in the EU was only [redacted] with the remainder receiving docetaxel, for which there is only about a [redacted] month gain in median OS for nivolumab.

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

The company did seem to include all relevant controlled trials given that the inclusion criteria were broad enough not to exclude on the basis of design or any of the comparators. However, it appears that there is only one RCT that at least approximately matches the population in the scope i.e. CheckMate 141. Unfortunately, it lacks any comparison with one of the comparators defined in the NICE scope, i.e. paclitaxel. Also, it does have some significant limitations, including a comparison not with the comparators in the scope, but with IC, which permits clinician choice of treatment. This therefore means that the ITT analysis prevents an unbiased estimate of the effectiveness of nivolumab versus any of the comparators. It did, however, show a statistically significant advantage in OS versus IC, which might be considered an unbiased estimate versus standard care, but only if IC was made on the same basis as that in clinical practice. However, there is no way of knowing that and it would have to mean that precisely the same proportion of patients was eligible for each of the therapies (methotrexate, docetaxel and cetuximab) as in the trial. To compound the problem, one of the choices was cetuximab, which is not in the scope. Therefore, the ERG considers that the representativeness of the CheckMate 141 trial to clinical practice in the United Kingdom (UK) is highly questionable most particularly in terms of patient characteristics that would determine both intended treatment and prognosis.

The ERG did ask in the clarification letter for analyses to attempt to overcome these two main limitations, i.e. the inclusion of cetuximab and the missing comparison with paclitaxel. In response, the company did demonstrate little effect of the removal of the cetuximab patients, which was likely given the small number (n=15). They also provided three tables, which summarised the design, baseline characteristics and outcomes of five paclitaxel trials. The ERG concluded that, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab. Also, the response to a clarification question regarding the difference in the HRs for OS between the European Union and North America highlighted the difference in percentage receiving each of the treatments in the scope (docetaxel and methotrexate). The ERG would therefore conclude that, whilst it is reasonable to believe that nivolumab extends life expectancy, it is impossible to be confident by how much in comparison to any treatment in the scope or which is considered to be standard care in the UK.

The company base-case ICERs (probabilistic) of nivolumab (with PAS) compared with docetaxel, paclitaxel and methotrexate were £35,157, £35,025 and £35,091 respectively. The ERG has incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate respectively. The most influential adjustments/corrections made by the ERG were 1) using a generalised-gamma distribution for estimating TTD; 2) using treatment independent utilities for PFS and PD health state utility values and; 3) using a dose and frequency of administration for docetaxel (75 mg/m2 Q3W) consistent with UK clinical practice. Moreover, in an exploratory analysis, the ERG used an adjusted dosage for nivolumab (fixed dose of 240 mg every two weeks) that was recently recommended by the FDA for renal-cell carcinoma, metastatic melanoma, and non-small cell lung cancer. This exploratory analysis, which was performed conditional upon the ERG base-case, resulted in ICERs (with PAS) of £50,160 - £53,439. Moreover, applying shorter time horizons, to explore the impact of the extrapolating estimated benefits of costs, resulted in increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year).

The equivalence assumptions between docetaxel and methotrexate as well as between docetaxel and paclitaxel can be questioned. However, a scenario analysis, provided by the company, using treatment specific effectiveness estimates for docetaxel and methotrexate (instead of using IC effectiveness), showed that the assumption of equivalence between docetaxel and methotrexate is not likely to be influential in terms of incremental QALYs, incremental costs and the ICER. To examine the assumption of equivalence between docetaxel and paclitaxel, the ERG performed a threshold analysis (conditional on the deterministic ERG base-case). This analysis indicated that if paclitaxel is more effective than docetaxel in terms of OS and PFS, up to a HR of approximately 0.93, nivolumab would not be cost effective compared with paclitaxel (assuming a threshold of £50,000 per QALY). Additionally, the cost effectiveness of nivolumab versus paclitaxel is uncertain given that, in Section 4.4, it is concluded there is some evidence, albeit weak, that paclitaxel is possibly more effective than nivolumab.

In conclusion, given the ERG base-case ICERs are estimated to be around £50,000 per QALY gained the large uncertainty regarding extrapolation and post-progression benefits in combination with the lack of external validation of long-term outcomes and the doubt about the generalisability of the CheckMate 141 trial results to the UK the decision, uncertainty around the cost effectiveness of nivolumab remains substantial.

8.2 Strengths and limitations of the assessment

The searches in the CS were well documented and easily reproducible; searches were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[84] Significant differences were noted between the original clinical effectiveness strategy and that used for the 2015 update. The MEDLINE and Embase searches were limited to English language only, which may have introduced a language bias. Separate adverse events searches were not conducted.

The ERG identified two issues which might limit the generalisability of results of the CheckMate 141 trial.

1. Based on information in the CS and the response for request for clarification, the prevalence of males in the index population is approximately 70%. It should be noted that 83.1% of the trial population is male. Given that discrepant results are reported for OS (nivolumab versus IC; HR 0.65 (95% CI 0.48 to 0.88) and 0.93 (95% CI 0.47 to 1.85) for males and females, respectively), this issue might influence the applicability of study results to the overall UK population.
2. The ERG noticed differences in the OS HRs between participants from North America and the European Union (EU), i.e. 0.55 (95% CI 0.36 to 0.85) and 0.91 (95% CI 0.62 to 1.33), respectively. In response to request for clarification, the company offered several explanations, including the lower proportion of human papillomavirus (HPV)-positive and never smoker patients in Europe, an imbalance of HPV status across treatment arms within the European subgroup and differences in choice of IC of therapy. Differences in the recorded baseline characteristics between the EU and North America as well as in the treatments chosen highlights the potential for lack of applicability to the UK.

The economic model structure is similar to other oncology assessments, similar to previous nivolumab appraisals and seems appropriate for the current decision problem. Moreover, the ERG considered the statistical methods used by the company for selecting the distributions for the time-to event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis.

In the economic model, the reliance on an equal effectiveness assumption for all comparators (i.e. docetaxel, methotrexate and paclitaxel) was considered as one of the main weaknesses. Moreover, the approach to modelling AEs was not reflective of best practices.

8.3 Suggested research priorities

Research that examines the relative effectiveness of paclitaxel in comparison to nivolumab, docetaxel and/or methotrexate would be valuable. Given the reliance of the estimate of survival on extrapolation of over 10 years based on follow-up of less than 18 months, the ERG would strongly recommend that follow-up continue of CheckMate 141 trial patients. A register would also be useful. Moreover, a NICE DSU Technical Support Document should be made available regarding the most appropriate methods for dealing with missing data for the health economic evaluations (e.g. resource use data or utility data) as well as the longitudinal analyses of health state utility data.

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Appendix 1: Further critique of searches in the company submission

Clinical effectiveness

- The ERG noted inclusion of search phrases with incorrect punctuation for some of the comparators, which the Ovid interface was unable to process correctly; e.g. (from line 78 of the Embase/MEDLINE update strategy on page 13):[13]

  "n methyl 2 [3 [2 (2 pyridyl)vinyl] 1h indazol 6 ylsulfanyl]benzamide" or "n methyl 2 [[3 [2 (2 pyridinyl)ethenyl] 1h indazol 6 yl]thio]benzamide" or " n methyl 2 [[3 [2 (pyridin 2 yl)ethenyl] 1h indazol 6 yl]sulfanyl]benzamide"

Appendix 2: Details ERG analyses (for validation purposes)

Fixing errors

1. Fixing errors consisted of:
    a. Adding OS, PFS and TTD as probabilistic parameters in the PSA (without incorporating the correlation between parameters)
    Incorporated in company revised base-case
    b. Incorporate NHS reference costs in PSA using upper and lower quartiles
    Incorporated in company revised base-case
    c. Changing the standard deviation into standard error for utility scores in the PSA
    'Utility Inputs'!G11:M12
    d. Using all available baseline utility data
    'Utility Inputs'!G11:M12

Fixing violations

2. Adding adverse event costs (£418.91) and disutility (-0.15) for pneumonitis
    Settings!G65
3. Using docetaxel dosing conform UK clinical practice
    Settings!G55

Matters of judgment

4. Using the generalised-gamma distribution for TTD
    TTD!K8
    TTD!M428
5. Using treatment independent utility
    'Utility Inputs'!G11:M12
6. Using treatment independent proportions for subsequent treatments
    'Data Store'!BK57:BW59
    Settings!G47

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 8 November 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Major comments

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the document it is stated that (based on the response to the clarification letter) the company believe that the population considered in the scope of the appraisal should be modified to include only patients who have progressed within six months of following platinum-based therapy. On page 12: "According to the response to the clarification letter, the Evidence Review Group (ERG) understands that the company believes that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy…" On page 27: "The ERG therefore interprets this to mean that the company believes that the scope should be modified to include only patients who have progressed within six	On page 12: "Following the company's response to the clarification letter, it is the Evidence Review Group (ERG)'s interpretation that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy...." On page 27: "The ERG therefore interprets this to mean that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy." On page 61: "Based on the company response to a clarification question regarding the representativeness of the CheckMate141 trial, the ERG's interpretation is that it would be reasonable for the scope to be modified to include only patients who have progressed within six months following platinum-based therapy."	That the scope should be modified is not the belief of Bristol-Myers Squibb and nor was this explicitly or implicitly stated in the Company Evidence Submission or the response to the clarification letter. The response to the clarification letter instead explained why the trial population is consistent with the population scope as it currently stands (i.e., "after platinum-based therapy"). Wording in the ERG report should therefore be amended to clarify that this is the ERG's interpretation and not the explicit view of Bristol-Myer's Squibb.	We thank the company for providing this clarification and the ERG report has been amended accordingly.

months following platinum-based therapy." On page 61: "Based on the company response to a clarification question regarding the representativeness of the CheckMate141 trial, the company seems to believe that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy. The ERG considers this to be reasonable."			

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The strength of evidence on which the claim that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab should be provided each time this claim is made. On pages 17, 61, 62, 74, 116: "…there does seem to be some evidence that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab."	This should be amended to: "…there does seem to be some evidence, albeit weak, that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab."	The ERG acknowledge that the evidence presented to support this claim is not particularly strong (i.e., based on phase II trials and single-arm studies with smaller patient numbers): See pages 22, 111 and 117 of the ERG report: "…there is some evidence, albeit weak, that paclitaxel is possibly more effective than nivolumab" In order to provide sufficient context in which to consider this	Although this is not a factual inaccuracy, for consistency, the ERG report has been amended accordingly (Edit has been made on page 117 and not page 116).

		claim and for consistency throughout the report, it is proposed that the amended wording should be added each time this claim is made.	

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The probabilities of nivolumab being cost-effective at specified willingness-to-pay thresholds, with the PAS applied for nivolumab, appear to have been derived from the 'without PAS' cost-effectiveness acceptability curve (Figure 33 in the response to the clarification letter). On page 20–21: "In response to the clarification letter, the company provided cost effectiveness acceptability curves that considered all treatments simultaneously and showed that with the PAS, the probability that nivolumab is cost effective is [redacted] and [redacted] at thresholds of £30,000 and £50,000 per QALY respectively." On page 104: "The updated CEACs provided by the company considered all	On page 20–21: "In response to the clarification letter, the company provided cost effectiveness acceptability curves that considered all treatments simultaneously and showed that with the PAS, the probability that nivolumab is cost effective is approximately [redacted] and [redacted] at thresholds of £30,000 and £50,000 per QALY respectively." On page 104: "The updated CEACs provided by the company considered all treatments simultaneously, incorporated treatment effectiveness parameters stochastically (though the correlation between the parameters was not incorporated) and showed that with the PAS, the probability that nivolumab is cost effective is [redacted] and [redacted] at thresholds of £30,000 and £50,000 per QALY respectively (Figure 5.8)." On page 105:	Probabilities for the 'with PAS' analysis presented in the report should be derived from Figure 34 (with PAS) rather than Figure 33 (without PAS) in the response to the clarification letter. The results from the 'with PAS' analyses should be presented in preference to the results from the 'without PAS' analyses, as the results 'with PAS' are most relevant for decision making and, at NICE's request, are the results that are not marked as confidential in the Company Evidence Submission.	The probabilities of cost effectiveness of [redacted] and [redacted] have been replaced with [redacted] and [redacted] (Edit made on page 105 and not 104).

treatments simultaneously, incorporated treatment effectiveness parameters stochastically (though the correlation between the parameters was not incorporated) and showed that with the PAS, the probability that nivolumab is cost effective is [redacted] and [redacted] at thresholds of £30,000 and £50,000 per QALY respectively (Figure 5.8)." On page 105: Figure 5.8 is from the analysis without the PAS applied for nivolumab and has been mislabelled as the 'with PAS' analysis	Present the correct 'with PAS' figure – see Figure 34 in the response to the clarification letter		

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate reporting of data regarding the percentage of patients treated with methotrexate in North America On page 43: "Secondly, methotrexate was given to [redacted] patients in the EU versus [redacted] in North America"	The total number of patients who received IC therapy in North America should be corrected to '**44**,' as such the following changes are required: On page 43: "Secondly, methotrexate was given to [redacted] patients in the EU versus [redacted] in North America" On page 44:	Inaccurate reporting of data should be corrected. (see Table 13 of the Company Evidence Submission, page 26 of the response to the clarification letter, as well as Table 4.5 on page 41 of the ERG report, and the first bullet point on page 43) **Note:** given the similarity in percentages between the EU ([redacted])	The ERG acknowledges that the percentage of 61% is misleading in that it was not made clear that it was calculated after excluding those patients taking cetuximab. The text has therefore been amended to reflect this. However, the ERG does not agree that there is not an issue regarding

On page 44: "It therefore appears that there were fewer of these kinds of patients (■ versus ■) in the EU than in North America."	"It therefore appears that there were fewer of these kinds of patients (■ versus ■) in the EU than in North America."	and North America (■) as a result of this correction, the ERG may wish to reconsider the conclusion presented in the report regarding the generalisability of the CheckMate 141 trial and: "the difference in percentage receiving each of the treatments in the scope (docetaxel and methotrexate)" (See pages 17, 116, and 117 of the ERG report) Bristol-Myers Squibb recommend that this argument be removed from the discussion of generalisability	generalisability in that, of those patients not receiving cetuximab, more received methotrexate.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The report provides the ERG's rationale for considering the analysis of CheckMate 141 by intended therapy to be legitimate but does not provide the rationale for the approach taken in the Company Evidence Submission. Where results of the study are presented from the Company Evidence Submission, Bristol-Myers Squibb believe that it would be reasonable to include	On page 44: "The main clinical effectiveness results presented in the CS are for nivolumab versus the total IC comparator arm, reflecting the two randomisation groups of the CheckMate 141 trial. Where possible, results by agent for the IC arm are presented in this report as well. In the CS, the company note the small sample sizes, lack of statistical power and the breaking of randomisation associated with these analyses."	Additional wording has been suggested in order to accurately represent the company's approach to data presentation from the CheckMate 141 study and to provide the company's position (as given in the Company Evidence Submission, see Section 4.4) on the approach taken by the ERG with regards to analyses by intended therapy for the IC arm, for the purposes of balance.	Not a factual inaccuracy and so no change required.

the relevant points provided in the Company Evidence Submission with regards to the interpretation of these results. On page 44: "The main clinical effectiveness results presented in the CS are for nivolumab versus the total IC comparator arm, reflecting the two randomisation groups of the CheckMate 141 trial. Where possible, results by agent for the IC arm are presented as well."		In addition, this amendment would provide additional, relevant context from the Company Evidence Submission for the ERG's discussion on the "legitimacy" of these analyses.	

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A quote from Company Evidence Submission with regards to the end-of-life criteria has been taken out of context. On page 115: "On the second criterion (extension of life of at least three months), the ERG agrees with the company who highlighted "this extension in life is just below the 3 months that are normally required of therapies to meet the NICE end-of-life criteria.""	This should be amended to: "On the second criterion (extension of life of at least three months), the ERG agrees with the company's statement on the median OS results from CheckMate 141 specifically, which noted that "this extension in life is just below the 3 months that are normally required of therapies to meet the NICE end-of-life criteria.""	The sentence quoted by the ERG on page 115 precedes a sentence in which the difference in **median** OS between treatment arms is presented, as given in full on page 114 of the ERG's report. The reference to median OS specifically should be included in order to put the quote in context and avoid any misunderstanding as to whether the company believe that the second end-of-life criterion has been met. To clarify, although with this statement the company acknowledged that the median OS difference from CheckMate 141 was	Not a factual inaccuracy and so no change required.

		just below 3 months (a statement of fact) the company's assertion is that nivolumab does meet the end-of-life criterion of an extension to life of at least 3 months. The following bullet points in the Company Evidence Submission (again, presented on page 114 of the ERG's report) go on to describe how median OS does not necessarily capture the long-term survival benefits of a treatment for some patients and that mean OS is preferable. A preference for **mean** OS is consistent with the NICE end-of-life criteria (as defined on page 114 of the ERG's report). It is worth noting that in both the company base case model and the ERG's revised model, mean OS was predicted to be greater for nivolumab compared to IC by >3 months. Based on the values of mean OS from the model, Bristol-Myers Squibb believe that this end-of-life criterion has been met, as stated in the Company Evidence Submission (see page 114 of the ERG's report).	

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A scenario analysis has been included that uses a dose of nivolumab (240 mg flat dose) that is not consistent with the dose (3 mg/kg) for which an application for marketing authorisation has been made to the European Medicines Agency. For example, on page 22: "… in an exploratory analysis, the ERG used an adjusted dosage for nivolumab (fixed dose of 240 mg every two weeks)"	Reconsider whether the scenario analysis using the 240 mg flat dose is appropriate for inclusion in the report.	According to the marketing authorisation application to the European Medicines Agency, the dose for nivolumab is expected to be 3 mg/kg (see SmPC for nivolumab), in line with the licensed dose for other indications. The dose for which a marketing authorisation application has been made for the head and neck cancer indication should be used in economic analyses.	Not a factual inaccuracy and so no change required.

Minor comments

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG report
There is an omission of 'drug-related adverse events (AEs)' from the discussion of the safety profile of nivolumab. On pages 13 and 52: "Nivolumab was generally well tolerated by patients in CheckMate 141 compared to IC	This should be amended to: "Nivolumab was generally well tolerated by patients in CheckMate 141 compared to IC of therapy, with a lower proportion of patients receiving nivolumab experiencing Grade 3-4 drug-related and all-causality adverse events (AEs), serious adverse events (SAEs) and discontinuation due to AEs."	'Drug-related AEs' are a key safety parameter for comparing treatments and so should be included for completeness.	Not a factual inaccuracy and so no change required.

of therapy, with a lower proportion of patients receiving nivolumab experiencing Grade 3-4 all-causality adverse events (AEs), serious adverse events (SAEs) and discontinuation due to AEs."			

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report results from the cost-effectiveness model are reported without clear reference as to whether these results are for analyses in which the Patient Access Scheme for nivolumab has or has not been applied. On page 19: "In the company's base-case analysis (probabilistic), the increased QALYs and costs for nivolumab resulted in ICERs of £35,157, £35,025, and £35,091 versus docetaxel, paclitaxel and methotrexate, respectively" On page 19 and 110: "…when decreasing the nivolumab utility value for progressed disease in a	On page 19: "In the company's base-case analysis (probabilistic, with PAS for nivolumab), the increased QALYs and costs for nivolumab resulted in ICERs of £35,157, £35,025, and £35,091 versus docetaxel, paclitaxel and methotrexate, respectively." On page 19 and 110: "…when decreasing the nivolumab utility value for progressed disease in a sensitivity analysis, the ICER (without PAS for nivolumab) increased with almost £18,000." On page 20: "In conclusion, given the ERG base-case ICERs (with PAS) are estimated to be around £50,000 per QALY gained,…" On page 101: "In the company's base-case analysis, the increased QALYs and costs for nivolumab (with PAS) resulted in ICERs of £34,902,	Results of the cost-effectiveness analyses should be presented in the context of whether the PAS for nivolumab has been applied. It has been assumed that the threshold analysis for determining the treatment effectiveness of paclitaxel at which nivolumab is no longer cost effective is using the PAS for nivolumab. This would require confirmation from the ERG. With regards to the value of £18,000 (page 19 and 110), it appears as is if this has been derived from the without PAS tornado plots (see Figures 54 to 57 in the Company Evidence Submission), the ERG may wish to present the with PAS results as these are considered to be more relevant for decision making.	Not a factual inaccuracy. All ERG analyses are with PAS. This is for instance indicated in the paragraph(s) preceding the paragraph cited by the company. See for instance on page 19: The overall differences in costs between nivolumab with PAS and the comparators were largely (87%) due to higher drug acquisition costs for nivolumab. In the company's base-case analysis (probabilistic), the increased QALYs and costs for nivolumab resulted in ICERs of £35,157, £35,025, and £35,091 versus docetaxel, paclitaxel and methotrexate, respectively.

sensitivity analysis, the ICER increased with almost £18,000." On page 20: "In conclusion, given the ERG base-case ICERs are estimated to be around £50,000 per QALY gained,…" On page 101: "In the company's base-case analysis, the increased QALYs and costs for nivolumab resulted in ICERs of £34,902, £34,777 and £34,908 versus docetaxel, paclitaxel and methotrexate, respectively (Table 5.22)" "The base-case results using PSA… The ICERs were £35,157, £35,025 and £35,091 for nivolumab versus docetaxel, paclitaxel and methotrexate, respectively." On page 109-110: "The threshold analyses considering the assumption of equivalence between docetaxel and paclitaxel, indicated that for paclitaxel to be cost effective compared with nivolumab (at a threshold of £50,000 per QALY)... The shorter time horizons resulted in increased ICERs	£34,777 and £34,908 versus docetaxel, paclitaxel and methotrexate, respectively (Table 5.22)" "The base-case results using PSA (with PAS for nivolumab)… The ICERs were £35,157, £35,025 and £35,091 for nivolumab versus docetaxel, paclitaxel and methotrexate, respectively." On page 109-110: ""The threshold analyses considering the assumption of equivalence between docetaxel and paclitaxel, indicated that for paclitaxel to be cost effective compared with nivolumab (with PAS; at a threshold of £50,000 per QALY)…. The shorter time horizons resulted in increased ICERs versus nivolumab (with PAS) to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year) (…) Moreover, applying shorter time horizons to explore the impact of the extrapolating estimated benefits of costs resulted in increased ICERs versus nivolumab (with PAS) to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)." On page 111 (and page 117): "This analysis indicated that if paclitaxel is more effective than docetaxel in terms of OS and PFS, up to a HR of approximately 0.93, nivolumab would not be cost effective	Suggested changes to confidentiality highlighting for the presentation of results from cost-effectiveness analyses have been listed below (**see Issues 24 onwards**).	See also on page 22: The ERG incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of [redacted]49,848, £46,611 and £46,565 for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate respectively. However to be clearer, the following sentence "In conclusion, given the ERG base-case ICERs are estimated to be around £50,000 per QALY gained" Has been changed into: "In conclusion, given the ERG base-case ICERs (with PAS) are estimated to be around £50,000 per QALY gained,…" (Edit made on page 112 AND 118 and not 111 and 117).

versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year) (…) Moreover, applying shorter time horizons to explore the impact of the extrapolating estimated benefits of costs resulted in increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)" On page 111 (and page 117): "This analysis indicated that if paclitaxel is more effective than docetaxel in terms of OS and PFS, up to a HR of approximately 0.93, nivolumab would not be cost effective compared with paclitaxel (assuming a threshold of £50,000 per QALY). (…) In conclusion, given the ERG base-case ICERs are estimated to be around £50,000 per QALY gained,…" On page 116: "Moreover, applying shorter time horizons to explore the impact of the extrapolating estimated benefits of costs resulted in	compared with paclitaxel (with PAS; assuming a threshold of £50,000 per QALY). (…) In conclusion, given the ERG base-case ICERs (with PAS) are estimated to be around £50,000 per QALY gained,…" On page 116: "Moreover, applying shorter time horizons to explore the impact of the extrapolating estimated benefits of costs resulted in increased ICERs versus nivolumab (with PAS) to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)."		

increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)"			

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The report states that no resource use of cost searches were conducted. On page 21: "Of concern for the cost effectiveness review, no resource use or cost searches were conducted, and data were therefore not systematically retrieved."	This sentence should be removed entirely.	Searches for resource use or cost searches were conducted as part of the economic systematic literature review (SLR; as described in Section 5.1 of the Company Evidence Submission). Search terms related to cost and resource use were included in search strategy (see Appendix 6 that accompanied the Company Evidence Submission) and studies reporting cost/resource use data were specified in the inclusion criteria for the review (see Table 23 in the Company Evidence Submission). Data from the relevant cost/resource use studies were extracted and presented in Appendix 11 that accompanied the Company Evidence Submission.	This was corrected and the text now reads: "Of concern for the cost effectiveness review, separate 'Measurement and valuation of health effects' searches were not conducted. No search terms for health-related quality of life/HRQOL or specific QoL instruments were included in the cost search strategies. Systematic searching was not conducted to identify data relating to HRQOL."

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The report states that it was unclear as to the number of reviewers that were involved in the SLRs. On page 22: "In addition, it was unclear how many reviewers were involved in the systematic review to identify clinical effectiveness evidence. The lack of a second reviewer in systematic reviews can increase the risk of bias and error in the review."	This sentence should be removed entirely.	The study selection process is presented in the Company Evidence Submission for both the clinical and economic SLRs (see Sections 4.1 and 5.1) and includes information on the number of reviewers involved: "Both the title and abstract and the full-text screening were performed by two independent reviewers, with any disagreements resolved by a third independent reviewer, if necessary." (Page 37, Section 4.1) "Screening was undertaken by a single reviewer and then checked by a second, independent reviewer." (Page 91, Section 5.1)	The ERG thanks the company for identifying this inaccuracy and the sentence has been deleted.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG have cited information from the latest BAHNO guidelines to describe current treatment practices for patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). Further details are also provided in the	"The BAHNO guidance (page S187) also reveals that there is no standard care following progression on platinum therapy in R/M patients: "*Once patients have progressed on platinum based chemotherapy, the prognosis is extremely poor and there is no standard*	Relevant information from the recent BAHNO guidelines regarding the use of docetaxel, paclitaxel and methotrexate in current clinical practice should be included in the report.	Not a factual inaccuracy and so no change required.

guidelines that are highly relevant to the comparators included in the scope of this appraisal but these do not appear in the report. On page 24: "The BAHNO guidance (page S187) also reveals that there is no standard care following progression on platinum therapy in R/M patients: "*Once patients have progressed on platinum based chemotherapy, the prognosis is extremely poor and there is no standard second-line or third-line therapy for these patients*.""	*second-line or third-line therapy for these patients*" The BAHNO guidance (page S187) does however specify single agent taxanes (paclitaxel or docetaxel) or methotrexate as possible treatment options for these patients: "*For second- or third-line chemotherapy* [after progression on platinum-based therapy]*, single agent taxane (paclitaxel or docetaxel) or methotrexate has also been used in patients who still have relatively good performance status*."	This information supports the choice of these therapies (as detailed in the final scope), as relevant comparators for this appraisal.	

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The report presents only the percentage of patients receiving radiotherapy as a "*subsequent therapy*" for each arm in CheckMate 141 in the context of rates of both surgery and radiotherapy. On page 44: "Indeed, rates of surgery and radiotherapy are reported as	On page 44: "Indeed, rates of surgery and radiotherapy are reported as "*subsequent therapies*" in Appendix 3; although a lower proportion of patients received subsequent surgery compared to IC (0.4% versus 1.7%), it is clear that a higher percentage of nivolumab patients received subsequent radiotherapy (12.1% versus 9.9 %)."	Inaccurate reporting of data has been corrected. See Appendix 3 that accompanied the Company Evidence Submission. **Note**: caution is advised if combining these percentages (received surgery and received radiotherapy), as patients may	The ERG thanks the company for identifying this inaccuracy and the sentence has been amended.

"*subsequent therapies*" in Appendix 3 and it is clear that a higher percentage of nivolumab patients received this (12.1% versus 9.9 %)."		have received more than one subsequent therapy.	

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The wording in the report is not clear as to what was requested in the clarification letter (i.e. what "this" in the sentence below refers to) On page 44: "In the clarification letter (Question A3), the company were asked to explain this and perform exploratory analyses to try to control for the effect of subsequent therapy."	On page 44: "In the clarification letter (Question A3), the company were asked to explain the rules that existed in the protocol for taking subsequent therapies and to perform exploratory analyses to try to control for the effect of subsequent therapy."	Given the preceding sentences, it is not clear in the report what "this" refers to in the sentence for amendment. As such, the response to the clarification letter request could be misrepresented. The suggested amendment provides clarity on what was requested in the clarification letter, based on the response that is summarised in the report: "Their response was that the CheckMate 141 trial did not give guidance to investigators on the choice of subsequent therapy."	The ERG agrees that this can be better expressed and have amended the sentence.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ORR is described as being not statistically significantly higher with nivolumab versus IC without	On page 47:	That a pre-specified testing hierarchy was used should be	Not a factual inaccuracy and so no change required.

any context being provided as to the use of a pre-specified testing hierarchy and the order of this hierarchy. On page 47: "The objective response rate (ORR) was greater, albeit not statistically significantly, for nivolumab versus IC of therapy…"	"The objective response rate (ORR) was greater, albeit not statistically significantly (according to pre-specified testing hierarchy which placed ORR behind PFS), for nivolumab versus IC of therapy…"	noted when describing differences between treatment arms in ORR. As PFS was ahead of ORR in the hierarchy and no significant difference in PFS was found between treatment arms, ORR was not tested for significance. The confidence intervals for the odds ratio of ORR do not cross one (see Table 7.4-1 of the CSR).	

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The report states that the date of the updated search for the economic SLR (as part of the response to the clarification letter) was not provided. On page 64: "The strategy and database host used was not reported, and the date of the update search was not provided."	On page 64: "The strategy and database host used was not reported, and for the databases searches the date of the update search was not provided."	The date of the congress searches was provided in the response to the clarification letter (response to Question 2): "The conferences listed in Table 2 were additionally searched on 29th September 2016" This should be acknowledged in the report.	Not a factual error, however the ERG has reworded this section for clarity. The text now reads: "The date of the conference update searching was provided in the clarification response. The Embase and PubMed strategies, and Embase database host used for the update, were not reported. The dates of the Embase and PubMed update searches were not provided."

Inaccurate data reporting amendments

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate reporting of information regarding follow-up time points for patient-reported outcomes On page 12: “Results were presented for various follow-up times, but the company defined two time points: Follow-up 1 as last dose date to last dose date +58 days and Follow-up 2 as last dose date +59 days to last dose date +102 days” On page 15 and page 52 (footnote to Table 2 and Table 4.7): “Follow-up 1 = Last dose date -to Last dose date + 58 days; Follow-up 2 = Last dose date + 59 days to Last dose date +102 days”	The description of follow-up times should be as follows: On page 12: “Results were presented for various follow-up times, but the company defined two time points: Follow-up 1 as being 35 days from the last dose ±7 days or the date of discontinuation (± 7 days) if the date of discontinuation was greater than 35 days after last dose and Follow-up 2 as being 80 days (±7 days) from Follow-up 1.’ On page 15 and page 52 (footnote to Table 2 and Table 4.7): “Follow-Up Visit 1 was scheduled for 35 days from the last dose ±7 days or coincided with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose. Follow-Up Visit 2 was scheduled for 80 days (±7 days) from Follow-Up Visit 1.”	Inaccurate reporting of information should be corrected. (see footnote of Table 8 in the Company Evidence Submission and footnote of Table 5.1-1 in the Study Protocol (CSR)) **Note:** these time points were noted in the Company Evidence Submission as part of the description of the trial methodology. However, results were only presented in the Company Evidence Submission for time points up to Week 21 due to diminished patient numbers thereafter. Given the correction to the definition of each follow-up time point, the ERG may wish to consider presenting data from time points up to Week 21 instead, as these are considered to be more informative.	Not a factual inaccuracy. Indeed there is a footnote to Table 5.1-4 in the Clinical Protocol in the CSR that cites the dates mentioned by company in the FAC. However, the time points cited in the ERG report were taken from Table 4.3.11.1-1: Time Windows for EORTC QLQ-C30, EORTC QLQ-H&N-35 and EQ-5D Assessments in the CSR. Therefore no change made.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Clarity required regarding the n values used On page 12: "There were bigger differences at second follow-up, but numbers of patient included at second follow-up were very small (EORTC-QLQ-C30 Global health status: n=5 and n=2 for nivolumab and IC respectively; EORTC QLQ-H&N35 – Pain: n=6 and n=2…" It is not clear that the n values are referring to change from baseline (Table 2 ERG report, page 15)	The following correction should be made to the statement: "There were bigger differences at second follow-up, but the numbers of patient included at second follow-up were very small (**change from baseline**; EORTC-QLQ-C30 Global health status: n=5 and n=2 for nivolumab and IC respectively; EORTC QLQ-H&N35 – Pain: n=6 and n=2…"	Inaccurate reporting of information should be corrected. Additional wording has been suggested in order to provide clarity on what the n values are referring to, as the actual number of patients included at the second follow up differ from the change at baseline (see ERG report Table 2, page 15).	Not a factual inaccuracy and so no change required.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate reporting of data regarding confidence intervals for HR of death for cetuximab In Table 1 on page 14 (repeated in Table 4.6 on page 46): The confidence interval in Table 1 of the ERG report for HR in	The confidence interval should be changed to: 0.47 (0.22, **1.01**)	Inaccurate reporting of data should be corrected. (see Figure 17 in the Company Evidence Submission)	Corrected (Table 4.6 is on page 47).

cetuximab is incorrect (0.47 [0.22, **1.101**])			

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate reporting of data with regards to median overall survival with docetaxel in CheckMate 141 (all randomised patients). On page 61: "…versus 7.5 months for nivolumab, 5.1 months for IC and [redacted] months for docetaxel."	Median overall survival for docetaxel should be corrected as follows: "…versus 7.5 months for nivolumab, 5.1 months for IC and [redacted] months for docetaxel."	Inaccurate reporting of data should be corrected. (See Figure 7.2-2 of the CSR and Table 1 of the ERG report) **See Issue 50 for change to confidentiality highlighting**	Corrected.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate reporting of data with regards to estimated mean TTD (months) from the company base case model In Table 5.8 on page 81: 2-spline odds, mean TTD, IC: 3.3	Mean TTD (months) should be corrected as follows: 2-spline odds, mean TTD, IC: 3.**4**	Inaccurate reporting of data should be corrected. (See Table 35 of the Company Evidence Submission)	Not a factual inaccuracy and so no change required. This value was calculated by the ERG from the model submitted by the company. Formula in cell TTD!AN463: =SUM(AN467:AN727)/(365.25/28)*12

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate reporting of data with regards to the increase in ICERs between the alternative docetaxel dosing scenarios On page 103: "…instead of the docetaxel dosing as used in the CheckMate 141 trial, the ICER would increase by £2,800 to £37,978 for nivolumab (with PAS) versus docetaxel."	Increase in ICER should be corrected to: "…instead of the docetaxel dosing as used in the CheckMate 141 trial, the ICER would increase by **£3,076** to £37,978 for nivolumab (with PAS) versus docetaxel."	Increase in the (with PAS) ICER has been corrected so as to compare the **deterministic** base case ICER (£34,902) with the (deterministic) scenario analysis ICER (£37,978). Even when comparing to the probabilistic base case ICER (£35,157), a correction would be required (increase is £2,821) **See Issue 62 for change to confidentiality highlighting**	The £2,800 has been changed to approximately £3,000.(Edit made on page 104 and not 103)

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate table referencing. Table 4.9 on page 54: Referenced as "Table 19 and 20 of the CS" Table 5.23 on page 101: Referenced as "Table 54 of the CS"	Referencing should be amended as follows: Table 4.9 on page 54: Referenced as "Table 19 of the CS" Table 5.23 on page 101: Referenced as "Table **64** of the CS"	Inaccurate referencing should be corrected	Corrected (Table 4.9 is on page 55. Table 5.23 is on page 102).

Confidentiality highlighting amendments

ERG response: Issues 24 to 65 have all produced amendments in the form of CIC highlighting.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is required. Table 1 on page 14 (Replicated as Table 4.6 on page 46)	Commercial in Confidence highlighting should be added to all data reported in this table with the exception of HRs and CIs for death with nivolumab (overall survival) from the analysis by intended therapy (denoted by footnote[c]) **See Appendix at the end of the document**	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is required. Table 2 on page 15 (Replicated as Table 4.7 on page 52)	The following unpublished and commercially-sensitive data should be highlighted as Commercial in Confidence: Table 2 on page 15. All data for each of the outcomes (EORTC QLQ-C30 – Global health status; EORTC QLQ-H&N35 – Pain; EQ-5D – VAS) in the rows: • Follow-up 1 change from baseline • Follow-up 2 change from baseline **See Appendix at the end of the document**	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. Table 3 on page 16.	Remove all highlighting in Table 3.	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 17: "… (nivolumab versus IC; [redacted], respectively…"	Remove all highlighting in this sentence. "… (nivolumab versus IC; HR 0.65 (95% CI 0.48 to 0.88) and 0.93 (95% CI 0.47 to 1.85) for males and females, respectively…"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 17:	Remove all highlighting in this sentence. "…i.e. 0.55 (95% CI 0.36 to 0.85) and 0.91 (95% CI 0.62 to 1.33) …"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the

"…i.e. [redacted] and [redacted] …"		confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 29

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required On page 19: "…post-discontinuation was based on the CheckMate 141 trial (nivolumab [redacted] and IC [redacted]) whereas…" On page 93: "…CheckMate 141 (nivolumab [redacted] and IC [redacted], see CS Table 46)." On page 98: "These proportions were similar between treatment arms (nivolumab, [redacted] and IC [redacted])"	Remove all highlighting. On page 19: "…post-discontinuation was based on the CheckMate 141 trial (nivolumab 29.6% and IC 32.2%) whereas…" On page 93: "…CheckMate 141 (nivolumab 29.6% and IC 32.2%, see CS Table 46)." On page 98: "These proportions were similar between treatment arms (nivolumab, 29.6% and IC 32.2%)"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 30

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required.	Remove all highlighting in these sentences. On page 19:	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company

On page 19: "…ICERs of [redacted] versus docetaxel…" On page 101: "The base-case results using PSA… The ICERs were [redacted] for nivolumab…" On page 110 and page 116: "…nivolumab (with PAS) compared with docetaxel, paclitaxel and methotrexate were [redacted] respectively."	"…ICERs of £35,157, £35,025, and £35,091 versus docetaxel…" On page 101: "The base-case results using PSA (with PAS for nivolumab)… The ICERs were £35,157, £35,025 and £35,091 for nivolumab…" On page 110 and page 116: "…nivolumab (with PAS) compared with docetaxel, paclitaxel and methotrexate were £35,157, £35,025 and £35,091 respectively."	Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses. **See also Issue 4 for reference to with or without PAS.**

Issue 31

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 19: "…increased to £62,156 - £62,399 and £77,111 - £77,232 respectively." On page 102: "…to £62,156 - £62,399) and TTD (scenario 8, using 2-spline odds distribution for TTD; ICER increased to £77,111 - £77,232) and using treatment independent health-state utilities (scenario 12; ICER increased to £39,767 - £39,917)."	Remove all highlighting in these sentences. On page 19: "…increased to £62,156 - £62,399 and £77,111 - £77,232 respectively." On page 102: "…to £62,156 - £62,399) and TTD (scenario 8, using 2-spline odds distribution for TTD; ICER increased to £77,111 - £77,232) and using treatment independent health-state utilities (scenario 12; ICER increased to £39,767 - £39,917)."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses.

On page 110: "… the ICERs of nivolumab (with PAS) versus the comparators increased to £62,156 to £62,399 and £77,111 to £77,232 respectively."	On page 110: "… the ICERs of nivolumab (with PAS) versus the comparators increased to £62,156 to £62,399 and £77,111 to £77,232 respectively."	

Issue 32

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 19 and page 110: "…the ICER increased with almost £18,000."	Remove all highlighting in this sentence on page 19 and page 110. "…the ICER (without PAS for nivolumab) increased with almost £18,000."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses. **See also Issue 4 for reference to with or without PAS.**

Issue 33

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 21 and page 104:	Remove all highlighting in this sentence on page 21 and page 104.	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the

"the probability that nivolumab is cost effective is [redacted] and [redacted] at thresholds of £30,000 and £50,000 per QALY respectively"	"the probability that nivolumab is cost effective is 42% and 68% at thresholds of £30,000 and £50,000 per QALY respectively"	confidentiality highlighting in the ERG report also be revised, accordingly. **Percentages have been corrected, as described in Issue 2**

Issue 34

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 21, page 111 and page 117: "In conclusion, given the ERG base-case ICERs are estimated to be around £50,000 per QALY gained,"	Remove all highlighting in this sentence on page 21, page 111 and page 117. "In conclusion, given the ERG base-case ICERs (with PAS) are estimated to be around £50,000 per QALY gained,"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses. **See also Issue 4 for reference to with or without PAS.**

Issue 35

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 22: "The ERG base-case resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS)"	Remove all highlighting from these sentences. On page 22: "The ERG base-case resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS)" On page 108:	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

On page 108: "This resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS)…" On page 110 and page 116: "The ERG base-case resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS)"	"This resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS)…" On page 110 and page 116: "The ERG base-case resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS)"	This includes the presentation of unmarked ICERs for the with PAS analyses.

Issue 36

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 22: "This exploratory analysis, which was performed conditional upon the ERG base-case, resulted in ICERs (with PAS) of £50,160 to £53,439. Moreover, applying shorter time horizons, to explore the impact of the extrapolating estimated benefits of costs, resulted in increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)." On page 109: "… ICERs versus nivolumab (with PAS) of £50,160 to £53,439 (Table 6.2)." On page 110:	Remove all highlighting from this sentence. On page 22: "This exploratory analysis, which was performed conditional upon the ERG base-case, resulted in ICERs (with PAS) of £50,160 to £53,439. Moreover, applying shorter time horizons, to explore the impact of the extrapolating estimated benefits of costs, resulted in increased ICERs (with PAS) versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)." On page 109: "… ICERs versus nivolumab (with PAS) of £50,160 to £53,439 (Table 6.2)." On page 110: "…increased ICERs versus nivolumab (with PAS) to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)." On page 110 and page 116:	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses. **See also Issue 4 for reference to with or without PAS.**

"…increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)." On page 110 and page 116: "This exploratory analysis, which was performed conditional upon the ERG base-case, resulted in ICERs (with PAS) of £50,160 to £53,439. Moreover, applying shorter time horizons to explore the impact of the extrapolating estimated benefits of costs resulted in increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)."	"This exploratory analysis, which was performed conditional upon the ERG base-case, resulted in ICERs (with PAS) of £50,160 to £53,439. Moreover, applying shorter time horizons to explore the impact of the extrapolating estimated benefits of costs resulted in increased ICERs versus nivolumab (with PAS) to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year)."	

Issue 37

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is required. Table 4.5 on page 41–42	Commercial in Confidence highlighting should be added for all data (except 'n' numbers in the column heading), reported in the following columns: • Docetaxel (n=54) • Methotrexate (n=52) • Cetuximab (n=15) **See Appendix at the end of the document**	For consistency with the confidentiality highlighting in the Company Evidence Submission Appendix 4

Issue 38

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 43: "…investigator's choice therapies was [redacted] for males and [redacted] for females." On page 117: "…nivolumab versus IC; [redacted], respectively"	Remove all highlighting in these sentences. On page 43: "…investigator's choice therapies was 0.65 (95% confidence interval (CI) 0.48 to 0.88) for males and 0.93 (95% CI 0.47 to 1.85) for females." On page 117: "…nivolumab versus IC; HR 0.65 (95% CI 0.48 to 0.88) and 0.93 (95% CI 0.47 to 1.85) for males and females, respectively"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 39

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 43 and page 117: "…European Union (EU), i.e. [redacted] and [redacted]), respectively."	Remove all highlighting in this sentence. On page 43 and page 117: "…European Union (EU), i.e. 0.55 (95% CI 0.36 to 0.85) and 0.91 (95% CI 0.62 to 1.33), respectively."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 40

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is required. On page 44 – 45: "The nivolumab, cetuximab, and methotrexate Kaplan-Meier OS curves [redacted]. The nivolumab and docetaxel KM OS curves [redacted] after this time point.	Commercial in Confidence highlighting should be added as follows: "The nivolumab, cetuximab, and methotrexate Kaplan-Meier OS curves [redacted]. The nivolumab and docetaxel KM OS curves [redacted] after this time point.	Changes have been suggested for consistency with the confidentiality highlighting used for the figure in the ERG report (Figure 4.2 on page 49), that this text describes.

Issue 41

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is required. On page 45: "However, there appears to be some variation by individual therapy with nivolumab performing particularly well versus cetuximab (HR=[redacted]) as opposed to versus docetaxel (HR=[redacted])."	Commercial in Confidence highlighting should be added, as follows: "However, there appears to be some variation by individual therapy with nivolumab performing particularly well versus cetuximab (HR=[redacted]) as opposed to versus docetaxel (HR=[redacted])."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 42

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 45: "The company performed this analysis, the results of which were that the HR of death for nivolumab versus IC ([redacted]) were [redacted] to that observed in the primary analysis of OS (0.70; 0.51, 0.96), suggesting that the treatment effect of nivolumab versus IC is [redacted]."	To be highlighted as follows: "The company performed this analysis, the results of which were that the HR of death for nivolumab versus IC ([redacted]) were very similar to that observed in the primary analysis of OS (0.70; 0.51, 0.96), suggesting that the treatment effect of nivolumab versus IC is not affected by the type or timing of subsequent systemic therapy received in each treatment arm."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 43

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 49: "In total, [redacted] and [redacted] patients in the nivolumab and IC arms, respectively,…, as the PFS-defining event, and [redacted] and [redacted] patients in each arm had died prior to experiencing disease progression."	Remove all highlighting in this sentence. "In total, 139 and 71 patients in the nivolumab and IC arms, respectively,…, as the PFS-defining event, and 51 and 32 patients in each arm had died prior to experiencing disease progression."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 44

Description of problem	Description of proposed amendment	Justification for amendment
Academic in Confidence highlighting is not required. On page 51: "After 45 weeks of follow-up, [redacted] were eligible for on-study assessment…"	Remove all highlighting in this sentence. "After 45 weeks of follow-up, fewer than 10 patients were eligible for on-study assessment…"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 45

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 52: "…with [redacted] deaths having occurred in the all treated population.[25] In the all treated population, disease progression was the most common cause of death and was responsible for [redacted] deaths in the nivolumab arm and [redacted] deaths…"	Remove all highlighting in this sentence. "…with 210 deaths having occurred in the all treated population.[25] In the all treated population, disease progression was the most common cause of death and was responsible for 109/132 (82.5%) deaths in the nivolumab arm and 68/78 (87.2%) deaths…"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 46

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. Table 4.8 on page 53	Remove all highlighting in Table 4.8.	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 47

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 53:	Remove all highlighting in this paragraph. "The most frequently reported AEs of any cause in the nivolumab arm were fatigue (26.3%), nausea (19.1%),	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the

"The most frequently reported AEs of any cause in the nivolumab arm were fatigue ([redacted]), nausea ([redacted]), anaemia ([redacted]), decreased appetite ([redacted]), malignant neoplasm progression ([redacted]), and constipation ([redacted]) for any grade; and anaemia ([redacted]), dyspnoea ([redacted]), hyponatremia ([redacted]), dysphagia ([redacted]), and pneumonia ([redacted]) for grade 3-4.[25] In the IC arm, the most frequently reported AEs of any cause were anaemia ([redacted]), fatigue ([redacted]), nausea ([redacted]), diarrhoea ([redacted]), malignant neoplasm progression ([redacted]), and asthenia ([redacted]) for any grade; and anaemia ([redacted]), hyponatremia ([redacted]), neutropenia ([redacted]), fatigue ([redacted]), and pleural effusion ([redacted]) for grade 3-4.[25]"	anaemia (18.6%), decreased appetite (18.6%), malignant neoplasm progression (18.2%), and constipation (15.3%) for any grade; and anaemia (5.9%), dyspnoea (5.5%), hyponatremia (4.7%), dysphagia (3.8%), and pneumonia (3.8%) for grade 3-4.25 In the IC arm, the most frequently reported AEs of any cause were anaemia (33.3%), fatigue (32.4%), nausea (30.6%), diarrhoea (23.4%), malignant neoplasm progression (22.5%), and asthenia (21.6%) for any grade; and anaemia (8.1%), hyponatremia (8.1%), neutropenia (7.2%), fatigue (6.3%), and pleural effusion (4.5%) for grade 3-4.[25]"	confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 48

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. Table 4.9 on page 54	Remove all highlighting in Table 4.9.	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 49

Description of problem	Description of proposed amendment	Justification for amendment
Academic in Confidence highlighting is not required. Table 4.10 on page 55–56	Remove all highlighting in Table 4.10.	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 50

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is required. On page 61: "…versus 7.5 months for nivolumab, 5.1 months for IC and [redacted] months for docetaxel."	To be highlighted as Commercial in Confidence as follows: "…versus 7.5 months for nivolumab, 5.1 months for IC and [redacted] months for docetaxel."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. **See Issue 20 for data correction**

Issue 51

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is required. On page 74: "… the mean weight of patients in the current assessment is [redacted] kg and that a	To be highlighted as Commercial in Confidence as follows: "… the mean weight of patients in the current assessment is [redacted] kg and that a 240 mg dose corresponds to a mean weight of 80 kg."	Data presented have not yet been published and should thus be marked as Commercial in Confidence.

240 mg dose corresponds to a mean weight of 80 kg.”		

Issue 52

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is required. Figure 5.5 on page 82 and Figure 5.6 on page 83.	All figures showing extrapolated TTD on page 82 should be marked as Commercial in Confidence.	Data presented have not yet been published and should thus be marked as Commercial in Confidence. Estimation of mean TTD from these figures could allow estimation of the PAS given that with PAS ICERs are now presented.

Issue 53

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. Table 5.9 on page 84	Remove all highlighting in Table 5.9.	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 54

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. Table 5.11 on page 86	Highlighting can be removed for all data in rows from • Baseline, to	Confidence changes requested by NICE. To establish a consistency throughout the

	• Week 69 Data presented in subsequent rows should remain Commercial in Confidence: • Follow-up 1 and 2 • Follow-up 2 • Survival follow-up 1, 2, 3 and 4 **See Appendix at the end of the document**	document, some data are no longer Commercial in Confidence.

Issue 55

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting requires amending. On page 90: "This is indeed what is observed in the results presented in the response to the clarification letter: without PAS, [redacted] and with PAS the ICERs changed from about [redacted]. This increase corresponds to a difference of approximately [redacted] on the ICERs."	Highlighting should be amended, as follows: On page 90: "This is indeed what is observed in the results presented in the response to the clarification letter: without PAS, [redacted] and with PAS the ICERs changed from about £35,000 to about £41,000. This increase corresponds to a difference of approximately 15% on the ICERs."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses.

Issue 56

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 91: "…UK patients included in CheckMate 141 were not used in the base-case due to the small sample size (n=34)."	Remove all highlighting in this sentence. "…UK patients included in CheckMate 141 were not used in the base-case due to the small sample size (n=34)."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 57

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 93: "Only [redacted] patients in CheckMate 141 received subsequent…"	Remove all highlighting in this sentence. "Only two patients in CheckMate 141 received subsequent…"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 58

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is required. Table 5.20 on page 99	Commercial in Confidence highlighting should be added to all data in the following columns: • Nivolumab QALYs • Incremental QALYs	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

	See Appendix at the end of the document	Information on incremental QALYs could allow calculation of total costs with nivolumab in the with PAS analysis, which could allow back-calculation of the PAS.

Issue 59

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 101: "…the increased QALYs and costs for nivolumab resulted in ICERs of [redacted]…"	Remove all highlighting in this sentence. "…the increased QALYs and costs for nivolumab (with PAS) resulted in ICERs of £34,902, £34,777 and £34,908…"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses. **See also Issue 4 for reference to with or without PAS.**

Issue 60

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting requires amending for the presentation of cost-effectiveness results. Table 5.22 on page 101 (with PAS) Table 5.23 on page 101 (with PAS) Table 5.26 on page 108 (with PAS)	In Table 5.22 and Table 5.23 on page 101, Table 5.26 on page 108 and Table 6.1 on pages 112–113: Commercial in Confidence highlighting can be removed from the following results: • ICERs for nivolumab versus each comparator Commercial in Confidence highlighting should be added to the following results:	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses.

Table 6.1 on pages 112–113 (with PAS)	• Total QALYs with nivolumab • Incremental QALYs for nivolumab versus each comparator Commercial in Confidence highlighting should remain for the following results: • Total costs with nivolumab • Incremental costs for nivolumab versus each comparator **See Appendix at the end of the document**	

Issue 61

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 101: "Based on these pairwise comparisons, the company reported a ■ probability…"	Remove all highlighting in this sentence. "Based on these pairwise comparisons, the company reported a 70% probability…"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Issue 62

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 103: "…the docetaxel dosing as used in the CheckMate 141 trial, the ICER would	Remove all highlighting in this sentence. "…the docetaxel dosing as used in the CheckMate 141 trial, the ICER would increase by £3,076 to £37,978 for nivolumab (with PAS)..."	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

increase by [redacted] to [redacted] for nivolumab (with PAS)..."		This includes the presentation of unmarked ICERs for the with PAS analyses. **See Issue 22 for correction of data**

Issue 63

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. Figure 5.7 on page 103.	Remove all highlighting from this figure.	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses.

Issue 64

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 104: "…ranged from [redacted] for nivolumab (with PAS)…"	Remove all highlighting from this sentence. "…ranged from £33,756 to £34,286 for nivolumab (with PAS)…"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly. This includes the presentation of unmarked ICERs for the with PAS analyses.

Issue 65

Description of problem	Description of proposed amendment	Justification for amendment
Commercial in Confidence highlighting is not required. On page 108: "…has a probability of being cost-effective of [redacted] at…"	Remove all highlighting from this sentence. "…has a probability of being cost-effective of 13% and 53% at…"	Revisions have been made to confidentiality highlighting following a request by NICE. For consistency with the revised Company Evidence Submission, it is proposed that the confidentiality highlighting in the ERG report also be revised, accordingly.

Appendix

Table 1 and Table 4.6 (amended confidentiality highlighting)

Outcome[a]	Nivolumab (n=240)	IC (n=121)	Methotrexate (n=52)	Docetaxel (n=54)	Cetuximab (n=15)
Overall Survival					
Deaths, n (%)	133 (55.4)	85 (70.2)	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)	[redacted]	[redacted]	[redacted]
HR for death with nivolumab (97.73% CI; p-value)[b]	0.70 (0.51, 0.96; p=0.0101)		0.64 (0.43, 0.96)[c] [redacted]	0.82 (0.53, 1.28)[c] [redacted]	0.47 (0.22, 1.101)[c] [redacted]
1-year survival rate, % (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)	[redacted]	[redacted]	[redacted]
Progression-free survival[e]					
Events, n (%)	190 (79.2)	103 (85.1)	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	2.0 (1.9, 2.1)	2.3 (1.9, 3.1)	[redacted]	[redacted]	[redacted]
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)		[redacted]	[redacted]	[redacted]
6-month PFS rate, % (95% CI)	19.7 (14.6, 25.4)	9.9 (5.0, 16.9)	[redacted]	[redacted]	[redacted]

Source: Gillison 2016[27], Ferris 2016[26] and CheckMate 141 CSR (7th June 2016)[25]

Notes: [a] Results are presented from the initial database lock of 18th December 2015 for OS and from the database lock of 5th May 2016 for PFS and tumour response; [b] The pre-specified boundary for statistical significance required the p-value to be less than 0.0227, 95% CI were 0.53, 0.92; [c] Reported in CS (intended IC): Figure 17, page 71; [d] Reported in CSR (actual treatment): Figure 7.2-2, page 82. [e] Disease progression and tumour response were assessed by the investigator using RECIST version 1.1; [f] Reported in CSR (intended IC): Figure 7.3.1-1, page 89

CI = confidence intervals; CS = company submission; CSR = clinical study report; HR = hazard ratio; IVRS = interactive voice response system; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours; TTR = time to response

Table 2 and Table 4.7 (amended confidentiality highlighting)

	Nivolumab 3mg/kg (N=240)		Investigator's Choice (N=121)	
	N	**Mean (SD)**	**N**	**Mean (SD)**
EORTC QLQ-C30 – Global health status[a]				
Baseline	188	55.0 (23.64)	91	57.4 (21.21)
FOLLOW-UP 1[*]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
FOLLOW-UP 2[*]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
EORTC QLQ-H&N35 – Pain[b]				
Baseline	193	27.8 (27.84)	91	26.2 (27.43)
FOLLOW-UP 1[*]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
FOLLOW-UP 2[*]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
EQ-5D – VAS[c]				
Baseline	185	51.2 (27.34)	87	57.9 (29.42)
FOLLOW-UP 1[*]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
FOLLOW-UP 2[*]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				

Source: CheckMate 141 CSR (7th June 2016) [a] Table S.10.7; [b] Table S.10.9; [c]S.10.10

Notes: [*] All questionnaires completed at baseline and on-study have been assigned a time-point. In case a patient has two on-study assessments within the same window, the assessment closest to the time-point was used. And in the case of two assessments at a similar distance to the time-point, the latest one was chosen. In the event where the

	Nivolumab 3mg/kg (N=240)		Investigator's Choice (N=121)	
	N	Mean (SD)	N	Mean (SD)
patient had no assessment at all in a specific window, the observation was treated as missing for that time-point. Follow-up 1 = Last dose date -to Last dose date + 58 days; Follow-up 2 = Last dose date + 59 days to Last dose date +102 days CSR = clinical study report; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire; EORTC QLQ-H&N35 = European Organisation for Research and Treatment of Cancer head and neck questionnaire; EQ-5D = European Quality of Life-5 Dimensions; VAS = visual analogue scale				

Table 4.5 (amended confidentiality highlighting)

Characteristic	Nivolumab (n=240)	IC (n=121)	Docetaxel (n=54)	Methotrexate (n=52)	Cetuximab (n=15)
Demographics					
Age, median years (range)	59.0 (29–83)	61.0 (28–78)	[redacted]	[redacted]	[redacted]
Age categorisation, n (%)					
<65	172 (71.7)	76 (62.8)	[redacted]	[redacted]	[redacted]
≥65 and <75	56 (23.3)	39 (32.2)	[redacted]	[redacted]	[redacted]
≥75	12 (5.0)	6 (5.0)	[redacted]	[redacted]	[redacted]
Male, n (%)	197 (82.1)	103 (85.1)	[redacted]	[redacted]	[redacted]
Race, n (%)					
White	196 (81.7)	104 (86.0)	[redacted]	[redacted]	[redacted]
Black/African American	10 (4.2)	3 (2.5)	[redacted]	[redacted]	[redacted]
Asian	29 (12.1)	14 (11.6)	[redacted]	[redacted]	[redacted]
Other	5 (2.1)	0	[redacted]	[redacted]	[redacted]
Region, n (%)					
North America	101 (42.1)	44 (36.4)	[redacted]	[redacted]	[redacted]
Europe	109 (45.4)	62 (51.2)	[redacted]	[redacted]	[redacted]
Rest of the world	30 (12.5)	15 (12.4)	[redacted]	[redacted]	[redacted]
Tobacco use, n (%)					
Current/former	191 (79.6)	85 (70.2)	[redacted]	[redacted]	[redacted]
Never	39 (16.3)	31 (25.6)	[redacted]	[redacted]	[redacted]
Unknown	10 (4.2)	5 (4.1)	[redacted]	[redacted]	[redacted]
Disease characteristics					
Site of primary tumour, n (%)[b]					

Characteristic	Nivolumab (n=240)	IC (n=121)	Docetaxel (n=54)	Methotrexate (n=52)	Cetuximab (n=15)
Oral cavity	108 (45.0)	67 (55.4)	[redacted]	[redacted]	[redacted]
Pharynx	92 (38.3)	36 (29.8)	[redacted]	[redacted]	[redacted]
Larynx	34 (14.2)	15 (12.4)	[redacted]	[redacted]	[redacted]
Other	6 (2.5)	3 (2.5)	[redacted]	[redacted]	[redacted]
HPV p-16 status, n (%)					
Positive	63 (26.3)	29 (24.0)	[redacted]	[redacted]	[redacted]
Negative	50 (20.8)	36 (29.8)	[redacted]	[redacted]	[redacted]
Not tested[c]	127 (52.9)	56 (46.3)	[redacted]	[redacted]	[redacted]
Prior therapy					
Number of lines of prior systemic cancer therapy, n (%)					
1	106 (44.2)	58 (47.9)	[redacted]	[redacted]	[redacted]
2	80 (33.3)	45 (37.2)	[redacted]	[redacted]	[redacted]
≥3	54 (22.5)	18 (14.9)	[redacted]	[redacted]	[redacted]
ECOG PS (%)					
0	49 (20.4)	23 (19.0)	Not reported		
1	189 (78.8)	94 (77.7)			
≥ 2	1 (0.4)	3 (2.5)			
Not reported	1 (0.4)	1 (0.8)			

Source: CheckMate 141 CSR (7th June 2016) – Tables S.3.1a, S.3.3a and S.3.8a[25]

Notes: [a] The investigator had to indicate which IC agent he or she would use if the subject were randomised the IC arm. This information was recorded in the IVRS system prior to randomisation; [b] Each was not subcategorised to capture a more precise primary tumour site (e.g., oropharynx); [c] Baseline 'unknown' HPV status included 180 patients who were not tested (per protocol, HPV status testing was only required for patients with oropharyngeal disease), 2 patients whose sample was collected after baseline, and 1 nivolumab subject who was tested for HPV, but had a non-evaluable test result.

Characteristic	Nivolumab (n=240)	IC (n=121)	Docetaxel (n=54)	Methotrexate (n=52)	Cetuximab (n=15)
CSR = clinical study report; ECOG PS = Eastern Cooperative Oncology Group performance status; HPV= human papillomavirus; IC= investigator's choice; IVRS= interactive voice response system					

Table 5.11 (amended confidentiality highlighting)

Time point	Nivolumab (n=240)		IC (n=121)	
	N[a]	n (%)[b]	N[a]	n (%)[b]
Baseline	240	191 (79.6)	121	90 (74.4)
Week 9	131	103 (78.6)	57	35 (61.4)
Week 15	85	58 (68.2)	30	16 (53.3)
Week 21	58	48 (82.8)	14	7 (50.0)
Week 27	44	31 (70.5)	5	2 (40.0)
Week 33	30	21 (70.0)	3	2 (66.7)
Week 39	19	9 (47.4)	1	1 (100)
Week 45	15	11 (73.3)	0	0
Week 51	9	6 (66.7)	0	0
Week 57	5	3 (60.0)	0	0
Week 63	2	0 (0)	0	0
Week 69	2	2 (100)	0	0
Follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]

Time point	Nivolumab (n=240)		IC (n=121)	
	N[a]	n (%)[b]	N[a]	n (%)[b]
Survival follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 39 of the CS, Bristol-Myers Squibb – Additional Analyses of Data Collected in CheckMate 141. Data on File No.: OR NIVO 058[63]

Notes: a N = Number of subjects in study; b n = Number of questionnaires received; % = completion rate, where completion is defined as a non-missing response in at least 1 of EQ-5D dimensions: Mobility, Self Care, Activity, Pain, Anxiety and VAS; Follow-Up Visit 1 was scheduled for 35 days from the last dose ±7 days or coincided with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose. Follow-Up Visit 2 was scheduled for 80 days (±7 days) from Follow-Up Visit 1; Survival Follow-Up visits were scheduled for every 3 months after Follow-Up visit 2.

CS = company submission; EQ-5D-3L = 3-level EuroQoL-5 Dimensions; IC = investigator's choice; VAS = visual analogue scale

Table 5.20 (amended confidentiality highlighting)

Health state				
	Nivolumab QALYs	**IC QALYs[a]**	**Incremental QALYs**	**% of total increment**
PF	[redacted]	0.18	[redacted]	15%
PD	[redacted]	0.22	[redacted]	83%
AE disutility	[redacted]	-0.03	[redacted]	2%
Total	[redacted]	0.37	[redacted]	100%
	Nivolumab LYs	**IC LYs[a]**	**Incremental LYs**	**% of total increment**
PF	0.34	0.26	0.09	13%
PD	0.99	0.39	0.60	87%
Total	1.33	0.65	0.68	100%

Source: Based on Table 56 of the CS[1] and response to request for clarification question B12[11]

Note: [a] QALYs and LYs were equal for docetaxel, methotrexate and paclitaxel

AE = adverse event; CS = company submission; IC = investigator's choice; LY, life year; PD = progressive disease; PF = progression-free; QALY = quality-adjusted life year

Table 5.22 (amended confidentiality highlighting for with PAS results) – same applies to Table 5.23, Table 5.26 and Table 6.1

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	£12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	£12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	£12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908

Source: Based on Table 54 of the CS[1]

CS = company submission; ICER = incremental cost effectiveness ratio; LY = life-years; PAS = Patient Access Scheme; QALYs = quality-adjusted life years

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check. The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
12	Text changed: "Following the company's response to the clarification letter, it is the Evidence Review Group (ERG)'s interpretation that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy...."
14, 47	Table 1 and Table 4.6 corrected: hazard ratio for death for cetuximab: "0.47 (0.22, 1.01)"
17, 61, 62, 74, 117	Text changed: "…there does seem to be some evidence, albeit weak, that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab."
21	Text changed: "Of concern for the cost effectiveness review, separate 'Measurement and valuation of health effects' searches were not conducted. No search terms for health-related quality of life/HRQOL or specific QoL instruments were included in the cost search strategies. Systematic searching was not conducted to identify data relating to HRQOL."
21, 105	The probabilities of cost effectiveness of [redacted] and [redacted] have been replaced with [redacted] and [redacted]
22	Sentences removed: "In addition, it was unclear how many reviewers were involved in the systematic review to identify clinical effectiveness evidence. The lack of a second reviewer in systematic reviews can increase the risk of bias and error in the review."
27	Text changed: "The ERG therefore interprets this to mean that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy."
43	• "Secondly, methotrexate was given to [redacted] patients in the EU versus [redacted] in North America."
44	Text changed: "Indeed, rates of surgery and radiotherapy are reported as "subsequent therapies" in Appendix 3; although a lower proportion of patients received subsequent surgery compared to IC (0.4% versus 1.7%), it is clear that a higher percentage of nivolumab patients received subsequent radiotherapy (12.1% versus 9.9 %)."
44	Text changed: "In the clarification letter (Question A3), the company were asked to explain the rules that existed in the protocol for taking subsequent therapies and to perform exploratory analyses to try to control for the effect of subsequent therapy."
55	Table 4.8 referenced as "Table 19 of the CS"
61	Text changed: "Based on the company response to a clarification question regarding the representativeness of the CheckMate141 trial, the ERG's interpretation is that it would be reasonable for the scope to be modified to include only patients who have progressed within six months following platinum-based therapy."
61	Text changed: "…versus 7.5 months for nivolumab, 5.1 months for IC and [redacted] months for docetaxel."
64	Text changed: "The date of the conference update searching was provided in the clarification response. The Embase and PubMed strategies, and Embase database host used for the update, were not reported. The dates of the Embase and PubMed update searches were not provided."
102	Table 5.23 referenced as "Table 64 of the CS"

104	Text changed: “the ICER would increase by approximately £3,000…”
112, 118	Text changed: “In conclusion, given the ERG base-case ICERs (with PAS) are estimated to be around £50,000 per QALY gained,…”

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

According to the company submission (CS), the anticipated indication for nivolumab as a treatment for squamous cell carcinoma of the head and neck (SCCHN) is: *"Nivolumab (Opdivo®) is indicated for the treatment of recurrent or metastatic squamous-cell cancer of the head and neck after platinum-based therapy in adults"*. This is precisely the population in the scope issued by the National Institute for Health and Care Excellence (NICE).

However, there seems to be a mismatch between this and the main trial, CheckMate 141. Following the company's response to the clarification letter, it is the Evidence Review Group (ERG)'s interpretation that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy, which is consistent with the inclusion criteria for the trial.

The comparators listed in the decision problem are in accordance with the scope and they are those that are compared in the cost effectiveness analysis (CEA). The intervention and outcomes are also in line with the scope.

However, there were several deviations from the scope in the clinical effectiveness section. Firstly, the company provided no evidence as to the effectiveness of paclitaxel. Secondly, the main trial randomised patients either to nivolumab or to an 'investigator choice' (IC) arm, which allowed clinicians to decide which of three treatments to prescribe thus preventing an intention to treat (ITT) analysis of nivolumab versus any of the comparators individually. Thirdly, IC in the main trial also included cetuximab, which is not within scope. The effects of these deviations are summarised in Section 1.2.

According to the CS, *"an application for a marketing authorisation in Europe for the indication detailed in this submission was submitted to the EMA on* [redacted] *and a positive opinion from the CHMP is anticipated on* [redacted]*"*.

1.2 Summary of clinical effectiveness evidence submitted by the company

The evidence base for the clinical efficacy of nivolumab in the treatment of SCCHN consists of one randomised controlled trial (RCT), CheckMate 141. The company report that only this RCT was included in the systematic review as it was the only one that reported the efficacy of nivolumab.

CheckMate 141 was a phase III multicentre randomised, open-label, active-controlled, parallel group trial comparing the efficacy and safety of nivolumab with IC, which included choice at the clinician's discretion of docetaxel, methotrexate or cetuximab. The primary endpoint for the CheckMate 141 trial was overall survival (OS), which demonstrated a significant improvement in the nivolumab arm compared to the IC arm (hazard ratio (HR), 0.70 [97.73% confidence interval (CI) 0.51 to 0.96]; stratified (by prior cetuximab use) log-rank test p-value=0.0101). There was no statistically significant difference in progression free survival (PFS; HR 0.89, 95% CI 0.7 to 1.1). Table 1 shows a summary of effectiveness of nivolumab versus IC, as well as the individual treatments.

The CS and clinical study report (CSR) also report three quality of life (QoL) instruments: the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC General Cancer Module (QLQ-C30)), the EORTC Head and Neck Specific Module (QLQ-H&N35) and the European Quality of Life questionnaire (EQ-5D). Results were presented for various follow-up times, but the company defined two time points: Follow-up 1 as last dose date to last dose date +58 days and Follow-up 2 as last dose date +59 days to last dose date +102 days. Generally, differences between groups were minimal at first follow-up (Table 2). There were bigger differences

Table 1: Overview of clinical effectiveness results from CheckMate 141 – all-randomised population

Outcome[a]	Nivolumab (n=240)	IC (n=121)	Methotrexate (n=52)	Docetaxel (n=54)	Cetuximab (n=15)
Overall Survival					
Deaths, n (%)	133 (55.4)	85 (70.2)	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)	[redacted]	[redacted]	[redacted]
HR for death with nivolumab (97.73% CI; p-value)[b]	0.70 (0.51, 0.96; p=0.0101)		0.64 (0.43, 0.96)[c] [redacted]	0.82 (0.53, 1.28)[c] [redacted]	0.47 (0.22, 1.01)[c] [redacted]
1-year survival rate, % (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)	NR	NR	NR
Progression-free survival[e]					
Events, n (%)	190 (79.2)	103 (85.1)	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	2.0 (1.9, 2.1)	2.3 (1.9, 3.1)	[redacted]	[redacted]	[redacted]
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)		[redacted]	[redacted]	[redacted]
6-month PFS rate, % (95% CI)	19.7 (14.6, 25.4)	9.9 (5.0, 16.9)	NR	NR	NR

Source: Gillison 2016[27], Ferris 2016[26] and CheckMate 141 CSR (7th June 2016)[25]

Notes: [a] Results are presented from the initial database lock of 18th December 2015 for OS and from the database lock of 5th May 2016 for PFS and tumour response; [b] The pre-specified boundary for statistical significance required the p-value to be less than 0.0227, 95% CI were 0.53, 0.92; [c] Reported in CS (intended IC): Figure 17, page 71; [d] Reported in CSR (actual treatment): Figure 7.2-2, page 82. [e] Disease progression and tumour response were assessed by the investigator using RECIST version 1.1; [f] Reported in CSR (intended IC): Figure 7.3.1-1, page 89

CI = confidence intervals; CS = company submission; CSR = clinical study report; HR = hazard ratio; IVRS = interactive voice response system; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours; TTR = time to response

The ERG did ask in the clarification letter for analyses to attempt to overcome these two main limitations, i.e. the inclusion of cetuximab and the missing comparison with paclitaxel. In response, the company did demonstrate little effect of the removal of the cetuximab patients, which was likely given the small number (n=15). They also provided three tables, which summarised the design, baseline characteristics and outcomes of five paclitaxel trials. The ERG concluded that, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence, albeit weak, that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab. Also, the response to a clarification question regarding the difference in the HRs for OS between the European Union and North America highlighted the difference in percentage receiving each of the treatments in the scope (docetaxel and methotrexate). The ERG would therefore conclude that, whilst it is reasonable to believe that nivolumab extends life expectancy, it is impossible to be confident by how much in comparison to any treatment in the scope or which is considered to be standard care in the UK.

The ERG also identified two issues which might limit the generalisability of results of the CheckMate 141 trial.

1. Based on information in the CS and the response for request for clarification, the prevalence of males in the index population is approximately 70%. It should be noted that 83.1% of the trial population is male. Given that discrepant results are reported for OS (nivolumab versus IC; HR 0.65 (95% CI 0.48 to 0.88) and 0.93 (95% CI 0.47 to 1.85) for males and females, respectively), this issue might influence the applicability of study results to the overall UK population.
2. The ERG noticed differences in the OS HRs between participants from North America and the European Union (EU), i.e. 0.55 (95% CI 0.36 to 0.85) and 0.91 (95% CI 0.62 to 1.33), respectively. In response to request for clarification, the company offered several explanations, including the lower proportion of human papillomavirus (HPV)-positive and never smoker patients in Europe, an imbalance of HPV status across treatment arms within the European subgroup and differences in choice of IC of therapy. Differences in the recorded baseline characteristics between the EU and North America as well as in the treatments chosen highlights the potential for lack of applicability to the UK.

The ERG considered the company's claim to fulfil the end of life (EOL) criteria and concluded that the first criterion (life expectancy of less than 24 months) has probably been met. It is, however, less clear that the second criterion (extension of life of at least three months) has been met given an advantage of less than three months in terms of median survival, as detailed in the main body of the report.

1.4 Summary of cost effectiveness submitted evidence by the company

The company conducted systematic reviews to identify relevant cost effectiveness studies, health-related quality of life studies, resources and costs studies. The company did not identify any study investigating the cost effectiveness of nivolumab in the population of interest for the current decision problem, and hence developed a *de novo* model.

The company developed a cohort-based partitioned survival model consisting of three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. According to the company, the model structure represents the clinical pathway of care of R/M SCCHN treatment and is consistent with previous economic evaluations submitted to NICE in R/M SCCHN (technology appraisal 172, 2009) and other evaluations of nivolumab appraised by NICE (ID811, ID900). Costs

LY gain) is attributable to the period after disease progression has been confirmed. Moreover, 78% of the estimated LY gain is attributable to the period after treatment discontinuation. This implies that additional benefit continues to accrue to patients whose disease has progressed and/or to patients that no longer receive nivolumab. In response to the clarification letter, the company provided cost effectiveness acceptability curves that considered all treatments simultaneously and showed that with the PAS, the probability that nivolumab is cost effective is 42% and 68% at thresholds of £30,000 and £50,000 per QALY respectively.

The company mentioned that external and cross validation were not possible. The ERG believes that the lack of external validation of long-term outcomes hampers the interpretation of the CS, particularly given the lack of evidence to support the long-term post-progression benefits of nivolumab.

In conclusion, given the ERG base-case ICERs are estimated to be around £50,000 per QALY gained, the large uncertainty regarding extrapolation and post-progression benefits in combination with the lack of external validation of long-term outcomes and the doubt about the generalisability of the CheckMate 141 trial results to the UK the decision, uncertainty around the cost effectiveness of nivolumab remains substantial.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal. The CS and response to clarification provided sufficient details for the ERG to appraise the searches. Efforts were made to identify e-Pub ahead of print publications in PubMed for the clinical and cost effectiveness searches. Additional searches of conference proceedings were conducted.

Using broad inclusion criteria, the company identified a single RCT (CheckMate 141, n=361) which reported results for all outcomes defined in the scope defined by NICE.

The economic model structure is similar to other oncology assessments as well as similar to previous nivolumab appraisals and seems appropriate for the current decision problem. Moreover, the ERG considered the statistical methods used by the company for selecting the distributions for the time-to event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis.

1.6.2 Weaknesses and areas of uncertainty

The ERG was concerned about the language bias of restricting searches to English language only as this is not in line with current best practice. Significant differences were noted between the original and update searches for clinical effectiveness studies. As the ERG was unable to access Embase.com, it was not possible to determine whether this impaired the performance of the CS searches. There were limitations with the use of indexing terms on Embase.com searches, as strategies only used EMTREE. Although some mapping between indexing terms does take place on Embase.com it is possible that relevant MEDLINE indexing terms (MeSH) will not be included in the search, and potentially relevant records could be missed. Searches for adverse events were based on the clinical effectiveness search strategies which included study design filters. It is possible that relevant evidence may have been missed as a consequence of this. Of concern for the cost effectiveness review, separate 'Measurement and valuation of health effects' searches were not conducted. No search terms for health-related quality of life/HRQOL or specific QoL instruments were included in the cost search strategies. Systematic searching was not conducted to identify data relating to HRQOL.

determine both intended treatment and prognosis. Given that, it is impossible to be confident to estimate efficacy and safety compared to any treatment in the scope or standard care in the UK.

It should be noted that the quality assessment of CheckMate 141 identified a few issues which might influence the validity of the findings, i.e. the lack of blinding as well as imbalances in the drop-outs between treatment and comparator.

In the economic model, the reliance on an equal effectiveness assumption for all comparators (i.e. docetaxel, methotrexate and paclitaxel) was considered as one of the main weaknesses. Moreover, the approach to modelling AEs was not reflective of best practices.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate respectively. The most influential adjustments/corrections made by the ERG were 1) using a generalised-gamma distribution for estimating TTD; 2) using treatment independent utilities for PFS and PD health state utility values and; 3) using a dose and frequency of administration for docetaxel (75 mg/m^2 once every three weeks) consistent with UK clinical practice. Moreover, in an exploratory analysis, the ERG used an adjusted dosage for nivolumab (fixed dose of 240 mg every two weeks) that was recently recommended by the FDA for renal-cell carcinoma, metastatic melanoma, and non-small cell lung cancer. This exploratory analysis, which was performed conditional upon the ERG base-case, resulted in ICERs (with PAS) of £50,160 to £53,439. Moreover, applying shorter time horizons, to explore the impact of the extrapolating estimated benefits of costs, resulted in increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year).

To examine the assumption of equivalence between docetaxel and paclitaxel, the ERG performed a threshold analysis (conditional on the deterministic ERG base-case). This analysis indicated that if paclitaxel is more effective than docetaxel in terms of OS and PFS, up to a HR of approximately 0.93, nivolumab would not be cost effective compared with paclitaxel (assuming a threshold of £50,000 per QALY). Additionally, the cost effectiveness of nivolumab versus paclitaxel is uncertain given, as stated in Section 1.3, there is some evidence, albeit weak, that paclitaxel is possibly more effective than nivolumab.

According to the CS, *"an application for a marketing authorisation in Europe for the indication detailed in this submission was submitted to the EMA on* [redacted] *and a positive opinion from the CHMP is anticipated on* [redacted]*"*.

3.1 Population

As stated in Table 1 in the CS, the anticipated indication for nivolumab as a treatment for SCCHN is: *"Nivolumab (Opdivo®) is indicated for the treatment of recurrent or metastatic squamous-cell cancer of the head and neck after platinum-based therapy in adults"*.[1]

ERG comment: This is precisely the population in the scope issued by NICE.[7] However, there seems to be a mismatch between this and the main trial, CheckMate 141.[13].

As stated in Table 9 in the CS, one of the inclusion criteria in the trial is the following: *'Tumour progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (i.e. with radiation after surgery), primary (i.e. with radiation), recurrent, or metastatic setting.'*[1] This would imply exclusion of those who have progressed after six months, although this contradicts the CS where Figure 63 appears to show that patients are only eligible after receipt of a first line of platinum-based therapy for R/M disease if progression occurs after six months (and not within six months).[1]

The company was asked to explain this discrepancy in the clarification letter (Question A5).[10] In response, they explained that *"...it is likely that patients who have progressed after 6 months of receiving platinum-based therapy may then be re-treated with platinum-based therapy prior to receiving further systemic anti-cancer therapy. By stipulating in the inclusion criteria that patients must have progressed within 6 months of the last dose of platinum-based therapy, the CheckMate 141 trial included those patients for whom platinum-based therapy was no longer an option – i.e., patients with R/M SCCHN after platinum-based therapy. The trial population is therefore consistent with the expected marketing authorisation for nivolumab and the scope for this appraisal and reflects the patient population that is expected to receive nivolumab in clinical practice"*.[11]

The ERG therefore interprets this to mean that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy.

3.2 Intervention

The intervention in the CS is nivolumab (Opdivo®).

ERG comment: The intervention matches the scope issued by NICE.[7]

3.3 Comparators

The comparators listed in the decision problem (Table 3.1) are in accordance with the NICE scope and they are those that are compared in the cost effectiveness analysis (CEA).[1]

ERG comment: There were several deviations from the scope in the clinical effectiveness section.

- Firstly, the company provided no evidence as to the effectiveness of paclitaxel. They were asked to present a review of five studies of paclitaxel that met the inclusion criteria for their systematic review in the clarification letter (Question A9).[10] The company response is presented in Section 4.3.

- Secondly, the main trial randomised patients either to nivolumab or to an *"investigator choice"* arm, which allowed clinicians to decide which of three treatments to prescribe thus preventing an ITT analysis of nivolumab versus any of the comparators.[1]

ERG comment:

Patient characteristics

Baseline characteristics seem to be comparable between the two arms, although unsurprisingly, given the IC design, this is not the case between the various treatments (Table 4.5). For example, the percentage of patients who have received at least three lines of therapy is much higher for methotrexate than docetaxel.

There is also an issue of generalisability. According to page 30 of the CS, the ratio of males to females affected by SCCHN is 2.4:1, which would, assuming an equal mortality rate, imply a prevalence of approximately 70% male in the index population.[1] However, in the CheckMate 141 trial, 83.1% are male (Table 13 of the CS).[1] This discrepancy could have implications on the estimated effectiveness in that the CheckMate 141 clinical study report (CSR) shows a large difference due to gender. In Figure 7.2.1-1, the hazard ratio (HR) for OS of nivolumab versus individual investigator's choice therapies was 0.65 (95% confidence interval (CI) 0.48 to 0.88) for males and 0.93 (95% CI 0.47 to 1.85) for females.[25]

In the clarification letter (Question A6), the ERG asked the company to explain how the CheckMate 141 trial is representative of the population.[10] The company responded that the CS contained a mistake and that the ratio of males to females should be 2.24 and not 2.4.[11] However, the ERG estimates that this would make very little difference to prevalence and so the question would remain as to whether the trial is representative. On page 25 of the response to request for clarification, the company also stated that *"in other licensed indications, no concerns have been raised with regards to differing efficacy between males and females"*.[11]

However, the ERG would argue that this does not rule out there being a difference in efficacy in SCCHN. The company also responded that the CI for OS HR in females is wide and attribute this at least partly to the small number of females. Indeed the CI for females does overlap that for males. In conclusion, whilst there remain questions as to the gender ratio representativeness of the CheckMate 141 trial and about the consequences of any discrepancy, no firm conclusions can be drawn.

A further issue regarding generalisability regarded the inclusion of countries other than the UK. It was mentioned in the clarification letter (Question A7) by the ERG that there was a difference in the OS HRs between North America and the European Union (EU), i.e. 0.55 (95% CI 0.36 to 0.85) and 0.91 (95% CI 0.62 to 1.33), respectively.[10] The company responded by providing some evidence that might explain this difference.[11] This included the lower proportion of human papillomavirus (HPV)-positive and never smoker patients in Europe, an imbalance of HPV status across treatment arms within the European subgroup and differences in choice of IC of therapy. What seems to be clear is that there are differences both in the recorded baseline characteristics between the EU and North America and, perhaps more importantly, in the treatments chosen.

- Firstly, [redacted], which appears to be due to difference in clinical practice.
- Secondly, methotrexate was given to [redacted] patients in the EU versus [redacted] in North America.

Given that the underlying premise of IC is that treatments are intended to be given according to clinician judgement, it logically follows that the clinician is responding to some characteristics of the patient, whether recorded or not. Indeed, this is what the company states in the CS (page 32): *'The choice of therapy is often determined by the type of prior therapies received and overall patient*

fitness. For example, patients who have received prior treatment with a taxane will most likely receive methotrexate, as will patients with poor overall fitness and those who cannot tolerate docetaxel".[1]

It therefore follows that if [redacted] of EU patients would have been intended by their clinicians to receive methotrexate then [redacted] were the kind of patient who were believed by clinicians to require methotrexate (as opposed to docetaxel). It therefore appears that there were fewer of these kinds of patients [redacted] in the EU than in North America.

Quality

As shown in Table 4.2 above, the CheckMate 141 trial was lacking in quality in that it was open label and thus prone to bias. This was further compounded by the fact that clinicians were able to exercise their own judgment in both concomitant and treatment on progression (subsequent treatment). As it states in Table 4.3 above, surgery and radiotherapy were permitted. Indeed, rates of surgery and radiotherapy are reported as "subsequent therapies" in Appendix 3; although a lower proportion of patients received subsequent surgery compared to IC (0.4% versus 1.7%), it is clear that a higher percentage of nivolumab patients received subsequent radiotherapy (12.1% versus 9.9 %).[13] The percentage who received subsequent systemic therapy was lower for nivolumab (29.6% versus 32.2%), but the percentage who received *"experimental drugs"* and taxanes was higher for nivolumab (3.8% versus 1.7% and 11.7% versus 8.3% respectively). In the clarification letter (Question A3), the company were asked to explain the rules that existed in the protocol for taking subsequent therapies and to perform exploratory analyses to try to control for the effect of subsequent therapy.[10] Their response was that the CheckMate 141 trial did not give guidance to investigators on the choice of subsequent therapy.[11] The results of additional analyses are in Section 4.2.1.

Results of the study

The CheckMate 141 trial included the following outcome measures to assess the outcomes defined in the final scope (see Table 3.1):

- Overall survival
- Progression-free survival
- Health-related quality of life
- Adverse effects of treatment

These results are presented below. Efficacy analyses were performed using the ITT population. Evidence from the CheckMate 141 trial for each of these outcomes is presented below in separate tables.

Overall survival

An overview of clinical effectiveness results (OS and PFS) from CheckMate 141 for nivolumab and the total IC arm is presented in Table 4.6. The main clinical effectiveness results presented in the CS are for nivolumab versus the total IC comparator arm, reflecting the two randomisation groups of the CheckMate 141 trial. Where possible, results by agent for the IC arm are presented as well.

The primary endpoint for the CheckMate 141 trial was OS, which demonstrated a significant improvement in the nivolumab arm compared to the IC arm (HR, 0.70 [97.73% CI, 0.51 to 0.96]; stratified (by prior cetuximab use) log-rank test p-value = 0.0101). The company stated that this is equivalent to a 30% reduction in risk of death with nivolumab versus IC of therapy.[27]

At the time of the initial database lock (18 December 2015), median OS was higher in the nivolumab arm (7.5 months; 95% CI, 5.5 to 9.1) versus the IC arm (5.1 months; 95% CI 4.0 to 6.0), after a median follow-up of 5.3 months (range 0–16.8) and 4.6 months (range 0.0–15.2) for each treatment group, respectively.[27]

Table 4.2: Overview of clinical effectiveness results from CheckMate 141 – all-randomised population

Outcome[a]	Nivolumab (n=240)	IC (n=121)	Methotrexate (n=52)	Docetaxel (n=54)	Cetuximab (n=15)
Overall Survival					
Deaths, n (%)	133 (55.4)	85 (70.2)	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)	[redacted]	[redacted]	[redacted]
HR for death with nivolumab (97.73% CI; p-value)[b]	0.70 (0.51, 0.96; p=0.0101)		0.64 (0.43, 0.96)[c] [redacted]	0.82 (0.53, 1.28)[c] [redacted]	0.47 (0.22, 1.01)[c] [redacted]
1-year survival rate, % (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)			
Progression-free survival[e]					
Events, n (%)	190 (79.2)	103 (85.1)	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	2.0 (1.9, 2.1)	2.3 (1.9, 3.1)	[redacted]	[redacted]	[redacted]
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)		[redacted]	[redacted]	[redacted]
6-month PFS rate, % (95% CI)	19.7 (14.6, 25.4)	9.9 (5.0, 16.9)			

Source: Gillison 2016[27], Ferris 2016[26] and CheckMate 141 CSR (7th June 2016)[25]

Notes: [a] Results are presented from the initial database lock of 18th December 2015 for OS and from the database lock of 5th May 2016 for PFS and tumour response; [b] The pre-specified boundary for statistical significance required the p-value to be less than 0.0227, 95% CI were 0.53, 0.92; [c] Reported in CS (intended IC): Figure 17, page 71; [d] Reported in CSR (actual treatment): Figure 7.2-2, page 82 (See also Figure 4.2 below). [e] Disease progression and tumour response were assessed by the investigator using RECIST version 1.1[28]; [f] Reported in CSR (intended IC): Figure 7.3.1-1, page 89

CI = confidence intervals; CS = company submission; CSR = clinical study report; HR = hazard ratio; IVRS = interactive voice response system; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours; TTR = time to response

Table 4.3: All-cause AEs in ≥10% patients in either treatment arm in CheckMate 141

Adverse event, n (%)[a, b]	Nivolumab (n=236)		IC (n=111)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Total patients with an event	229 (97.0)	97 (41.1)	109 (98.2)	58 (52.3)
General disorders and administration site conditions	134 (56.8)	17 (7.2)	79 (71.2)	16 (14.4)
Fatigue	62 (26.3)	8 (3.4)	36 (32.4)	7 (6.3)
Pyrexia	30 (12.7)	1 (0.4)	16 (14.4)	3 (2.7)
Asthenia	24 (10.2)	5 (2.1)	24 (21.6)	4 (3.6)
Mucosal inflammation	8 (3.4)	0	17 (15.3)	2 (1.8)
Gastrointestinal disorders	129 (54.7)	19 (8.1)	73 (65.8)	11 (9.9)
Nausea	45 (19.1)	1 (0.4)	34 (30.6)	1 (0.9)
Constipation	36 (15.3)	2 (0.8)	20 (18.0)	0
Diarrhoea	35 (14.8)	2 (0.8)	26 (23.4)	3 (2.7)
Dysphagia	29 (12.3)	9 (3.8)	15 (13.5)	3 (2.7)
Vomiting	27 (11.4)	1 (0.4)	14 (12.6)	0
Respiratory, thoracic and mediastinal disorders	107 (45.3)	38 (16.1)	47 (42.3)	12 (10.8)
Cough	32 (13.6)	1 (0.4)	10 (9.0)	0
Dyspnoea	32 (13.6)	13 (5.5)	12 (10.8)	2 (1.8)
Metabolism and nutrition disorders	106 (44.9)	34 (14.4)	56 (50.5)	21 (18.9)
Decreased appetite	44 (18.6)	3 (1.3)	22 (19.8)	4 (3.6)
Hyponatraemia	22 (9.3)	11 (4.7)	14 (12.6)	9 (8.1)
Investigations	81 (34.3)	18 (7.6)	33 (29.7)	9 (8.1)
Weight decreased	31 (13.1)	0	16 (14.4)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	64 (27.1)	8 (3.4)	33 (29.7)	2 (1.8)
Malignant neoplasm progression	43 (18.2)	5 (2.1)	25 (22.5)	2 (1.8)
Skin and subcutaneous tissue disorders	62 (26.3)	1 (0.4)	40 (36.0)	8 (7.2)
Dry skin	11 (4.7)	0	12 (10.8)	0
Alopecia	2 (0.8)	0	14 (12.6)	3 (2.7)
Blood and lymphatic system disorders	58 (24.6)	22 (9.3)	44 (39.6)	20 (18.0)
Anaemia	44 (18.6)	14 (5.9)	37 (33.3)	9 (8.1)

Source: Table 19 of the CS[1]

Notes: [a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy. b AEs were coded using the MedDRA version 18.1 and were graded for severity according to the NCI CTCAE version 4.0; Database lock of 18th December 2015.

AE = adverse event; CS = company submission; IC = investigator's choice; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

'Select' AEs, defined as AEs with a potential immunological cause that are of special clinical interest with the use of nivolumab, were analysed according to organ category (skin, gastrointestinal,

As shown in Table 4.11, each of these studies is a trial of the treatment of interest i.e. paclitaxel and, in all but one study (Tahara 2011[39]), at the dose used in the economic analysis, i.e. 80 mg/m^2 once weekly. The population does vary between the studies, but the same four out of five studies might reasonable be considered to be in the population of interest to this appraisal, i.e. R/M SCCHN with prior platinum-based therapy.[7]

The baseline characteristics are shown in Table 4.12. Unfortunately, the studies vary in the completeness of reporting. Of the four most comparable studies, one reports virtually no characteristics.[37, 38] The other three do report probably sufficient characteristics to compare with the CheckMate 141 trial.[40-42]

Age seems comparable in all studies. In terms of gender, two studies, Caballero 2007 and Grau 2009a, are roughly comparable with the majority being male.[40, 41] Grau 2009b appears to be quite different with the majority being female.[42] The distribution of the site of the primary tumour is different to CheckMate 141, although the effect of this is difficult to predict. The most important reported difference is probably in terms of Eastern Cooperative Oncology Group performance status (ECOG PS). Although across all studies the majority of patients have a value of 1, in two studies, Caballero 2007 and Grau 2009a, a substantial minority have a value of 2, in contrast to the CheckMate 141 trial, where only four patients had this value.[40, 41] The importance of this is that it might mean that outcomes and OS in particular would be likely to be worse in the paclitaxel studies, at least those by Caballero 2007 and Grau 2009a.

Interestingly, despite the prediction that, according to ECOG PS, outcomes would be most likely to be worse in Caballero 2007 and Grau 2009a, they appear to be better than in the CheckMate 141 trial.[1, 40, 41] In particular, median OS was 8.5 months in Grau 2009a versus 7.5 months for nivolumab, 5.1 months for IC and [redacted] months for docetaxel.[41] Indeed, only in Grau 2009b, which is the population of mainly women, was the median OS close to that in the docetaxel group.[42] Unfortunately, OS was not reported in Cabellero 2007 and neither was PFS, although it was also longer in the other paclitaxel studies than in either nivolumab, IC or the docetaxel group. As shown in Table 4.13, ORR was much higher for paclitaxel in any study than IC, where it was only 7%, as reported in Table 16 in the CS.[1] It was also higher in both Cabellero 2007 and Grau 2009a than for nivolumab, although it was lower in the paclitaxel arm of BERIL-1.[37, 38, 40, 41]

In conclusion, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence, albeit weak, that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

This is not relevant given that there was no meta-analysis.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG included a detailed discussion of the paclitaxel trials that were identified in the CS (see Section 4.3).

4.6 Conclusions of the clinical effectiveness section

Based on the company response[11] to a clarification question[10] regarding the representativeness of the CheckMate141 trial, the company seems to believe that the scope should be modified to include only patients who have progressed within six months following platinum-based therapy. The ERG considers this to be reasonable.

The company did seem to include all relevant controlled trials given that the inclusion criteria were broad enough not to exclude on the basis of design or any of the comparators.[1] However, it appears that there is only one RCT that at least approximately matches the population in the scope i.e. CheckMate 141. Unfortunately, it lacks any comparison with one of the comparators i.e. paclitaxel. Also, it does have some significant limitations, including a comparison not with the comparators in the scope, but with IC, which permits clinician choice of treatment. This therefore means that the ITT analysis prevents an unbiased estimate of the effectiveness of nivolumab versus any of the comparators. It did, however, show a statistically significant advantage in OS versus IC, which might be considered an unbiased estimate versus standard care, but only if IC was made on the same basis as that in clinical practice. However, there is no way of knowing that and it would have to mean that precisely the same proportion of patients was eligible for each of the therapies (methotrexate, docetaxel and cetuximab) as in the trial. To compound the problem, one of the choices was cetuximab, which is not in the scope.[7] Therefore, the ERG considers that the representativeness of the CheckMate 141 trial to UK clinical practice is highly questionable most particularly in terms of patient characteristics that would determine both intended treatment and prognosis.

The ERG did ask in the clarification letter for analyses to attempt to overcome these two main limitations: inclusion of cetuximab and no comparison with paclitaxel.[10] In response, the company did demonstrate little effect of the removal of the cetuximab patients, which was likely given the small number (n=15).[11] They also provided three tables which summarised the design, baseline characteristics and outcomes of five paclitaxel trials. The ERG concluded that, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence, albeit weak, that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab. Also, the response to a clarification question regarding the difference in the HR for OS between the EU and North America highlighted the difference in percentage receiving each of the treatments in the scope (docetaxel and methotrexate). [11] The ERG would therefore conclude that, whilst it is reasonable to believe that nivolumab extends life expectancy, it is impossible to be confident by how much in comparison to any treatment in the scope or which is considered to be standard care in the UK.

language bias of restricting the searches to English language only; this is not in line with current best practice.[17, 18, 20-23]

The PubMed and Cochrane Library searches did not incorporate an English language limit, and following clarification, the company reported this restriction had been applied during screening.[11]

The company's economics searches were a year older than those included in the clinical effectiveness sections, however a partial update of Embase.com and PubMed was undertaken and screened in response to the clarification letter.[11] The company reported conducting an update search for Embase, PubMed and three conference proceedings, with the total number of records retrieved. The date of the conference update searching was provided in the clarification response. The Embase and PubMed strategies, and Embase database host used for the update, were not reported. The dates of the Embase and PubMed update searches were not provided.

The ERG considered the concurrent MEDLINE and Embase searches to be satisfactory in structure in addressing retrieval of economic evaluations and cost studies, however the English language limit may have introduced a language bias.

Measurement and valuation of health effects

The cost effectiveness searches reported in Section 5.1 and Appendix 6 of the CS were used to inform this section.[1]

ERG comment: The study design filters were not referenced and did not appear to be published objectively derived filters. The filters contained a combination of subject heading terms and free text terms to capture literature referring to costs, economics or utilisation, however no additional terminology to health-related quality of life (HRQoL) studies were included. The search would have greatly benefited from inclusion of additional indexing and free-text terms to identify quality of life, HRQoL and specific instruments, such as the EQ-5D or SF-36. The ERG therefore believes that although relevant data from the CheckMate 141 trial were included in the model, this approach does not meet with NICE requirements.[43] The ERG did not consider this approach appropriate, furthermore the same limitations concerning the simultaneous Embase.com search and the English language restriction also apply here.

Cost and healthcare resource identification, measurement and valuation

The cost effectiveness searches reported in Section 5.1 and Appendix 6 of the CS were used to inform this section.[1]

ERG comment: The study design filters were not referenced and did not appear to be published objectively derived filters. The filters contained a combination of subject heading terms and free text terms to capture literature referring to costs, economics or utilisation. The ERG considered this approach adequate, although the same limitations concerning the simultaneous Embase.com search and the English language restriction also apply here.

5.1.2 Inclusion/exclusion criteria used in the cost effectiveness review

Screening of publications by title and abstract was performed; followed by full publication review. Eligibility criteria for the review are presented in Table 5.1.

model, docetaxel is assumed to be administrated once weekly at a dose of 30 mg/m^2 while in the UK docetaxel is mostly administrated at a dose of 75mg/m^2 every three weeks, according to the company.[1]

In the IC comparator arm of the CheckMate 141 trial, the majority of patients received docetaxel or methotrexate (47% and 41% respectively), whilst the remaining patients received cetuximab.[26, 27] The company based OS, PFS, TTD, and incidence of AEs for docetaxel and methotrexate in the model on the total IC arm of the CheckMate 141 trial, assuming clinical equivalence between these therapies. The company states this assumption was confirmed by expert clinician feedback and by data from a phase II clinical trial.[5, 53] Furthermore, clinical equivalence was assumed between docetaxel (as observed in the IC arm of the CheckMate 141 trial) and paclitaxel. The company states that this assumption is supported by UK clinical opinion,[5, 9, 52] and necessary because of limited RCT evidence (Section 4.3) for paclitaxel as a monotherapy for the treatment of platinum refractory R/M SCCHN.

ERG comment: The ERG will successively address the following issues: the dosing of nivolumab, the administration schedule and dosing of docetaxel and the equivalence assumptions between docetaxel and paclitaxel and between docetaxel and methotrexate.

The dosing schedule of nivolumab has recently been modified by the US Food and Drug Administration (FDA) from the 3 mg/kg every two weeks to a 240 mg (fixed) dose every two weeks for the treatment of renal cell carcinoma, metastatic melanoma and non-small cell lung cancer.[54] The FDA does not expect this new dose regimen to have efficacy or safety consequences. If the same administration scheme modification takes place in Europe and is also considered relevant for R/M SCCHN, this might increase the acquisition costs (and consequently the cost effectiveness outcomes) of nivolumab since the mean weight of patients in the current assessment is [redacted] kg and that a 240 mg dose corresponds to a mean weight of 80 kg. The influence of this assumption will be explored in a scenario analysis (see Section 5.3)

The administration schedule of docetaxel applied in the model is not representative of UK daily practice. Therefore, the ERG will use the once every three week administration schedule of docetaxel (75 mg/m^2 per administration) instead of the once weekly administration schedule (30 mg/m^2 per administration) in its base-case analysis because this schedule is more routinely used in the UK and because there is no evidence to support a difference in efficacy between the two docetaxel schemes (response to Clarification Question A8).[11]

In the CS, clinical equivalence between docetaxel and paclitaxel was not supported by clinical evidence. The ERG consequently requested clarification on the justification of this assumption. The company explained that the sources used represent the opinion of two UK clinicians and from an international advisory board.[9, 51, 52] The two UK clinicians emphasised the lack of evidence demonstrating a difference in effectiveness between docetaxel and paclitaxel. However, there is no empirical evidence which supports this assumption. Consequently, uncertainty remains concerning this assumption. The ERG will however maintain this assumption in its base-case since there is no clinical evidence contradicting this assumption or to inform plausible alternative scenario analyses. Moreover, the performance of a systematic search plus network meta-analysis was not feasible for the ERG within the timelines. However, as concluded in Section 4.3, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence, albeit weak, that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab. Therefore, a threshold analysis (conditional upon the ERG base-case) will be performed to determine what the relative

In the company's base-case analysis, the increased QALYs and costs for nivolumab resulted in ICERs of £34,902, £34,777 and £34,908 versus docetaxel, paclitaxel and methotrexate, respectively (Table 5.22).

Table 5.4: Deterministic company base-case results (nivolumab with PAS)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Nivolumab	[redacted]	1.33	[redacted]				
Docetaxel	£12,538	0.65	0.37	[redacted]	0.68	[redacted]	£34,902
Paclitaxel	£12,603	0.65	0.37	[redacted]	0.68	[redacted]	£34,777
Methotrexate	£12,535	0.65	0.37	[redacted]	0.68	[redacted]	£34,908

Source: Based on Table 54 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LY = life-years; PAS = Patient Access Scheme; QALYs = quality-adjusted life years

5.2.11 Sensitivity analyses

The company presented probabilistic sensitivity analysis (PSA), deterministic sensitivity analysis (DSA) and deterministic scenario analysis.

Probabilistic sensitivity analysis

The base-case results using PSA (1,000 simulations) are presented in Table 5.23 and resulted in slightly higher ICERs than those presented for the deterministic company base-case. The ICERs were £35,157, £35,025 and £35,091 for nivolumab versus docetaxel, paclitaxel and methotrexate, respectively.

Table 5.5: Probabilistic company base-case results (nivolumab with PAS)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Nivolumab	[redacted]	[redacted]			
Docetaxel	£12,544	0.37	[redacted]	[redacted]	£35,157
Paclitaxel	£12,613	0.37	[redacted]	[redacted]	£35,025
Methotrexate	£12,576	0.37	[redacted]	[redacted]	£35,091

Source: Based on Table 64 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; PAS = Patient Access Scheme; QALYs = quality-adjusted life years

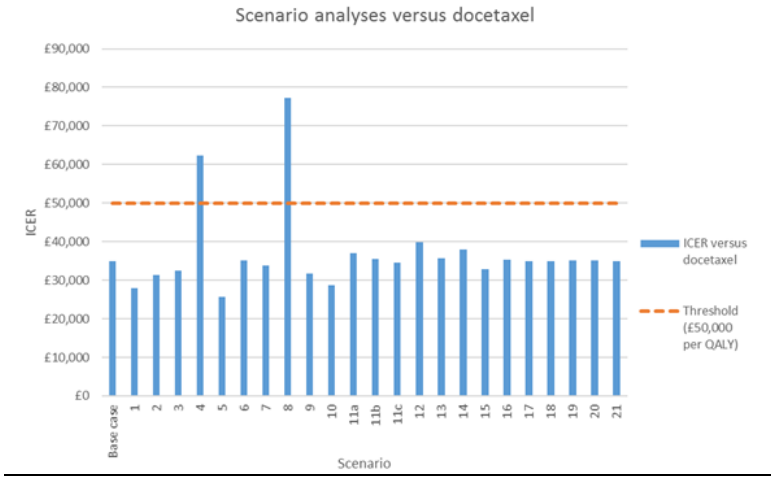
The company provided incremental cost effectiveness planes and cost effectiveness acceptability curves (CEACs; CS Figures 42-53) using pairwise comparisons of nivolumab versus the comparators (instead of comparing all comparators simultaneously). Based on these pairwise comparisons, the company reported a 70% probability of nivolumab (with PAS) being cost effective at a threshold of £50,000 per QALY.

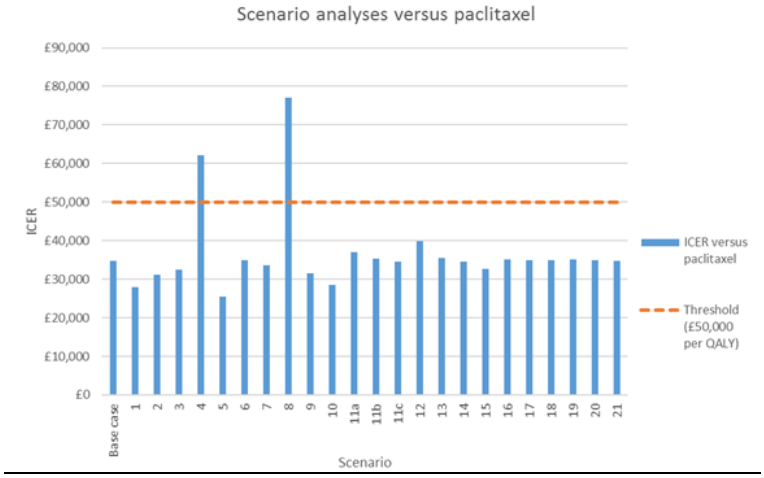
Deterministic sensitivity analysis

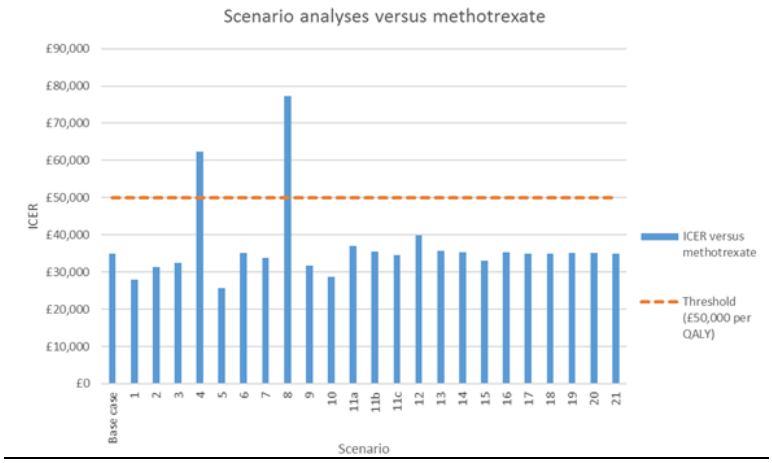
The company conducted DSA by varying all parameters for which there were single input values into the model by ±15% of their mean value in order to identify key model drivers. The company acknowledged that the parametric distributions chosen to model treatment effectiveness (i.e. OS, PFS and TTD) were not captured in the deterministic sensitivity analysis.

calculate docetaxel treatment costs, instead of the docetaxel dosing as used in the CheckMate 141 trial, the ICER would increase by approximately £3,000 to £37,978 for nivolumab (with PAS) versus docetaxel.

Figure 5.1: Scenario analyses presented in the CS considering nivolumab with PAS







Source: Based on Figures 60-62 of the CS[1]

CS = company submission; ICER = incremental cost effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year

ERG comment: Given that PFS was similar between nivolumab and IC while nivolumab resulted in a clinically relevant median OS benefit, a post-progression benefit of nivolumab is to be expected.

However, it is noteworthy that in the CS base-case the majority (83%) of the estimated QALY gain (87% of the estimated LY gain) is attributable to the period after disease progression has been confirmed. Moreover, 78% of the estimated LY gain is attributable to the period after treatment discontinuation. This implies that additional benefit continues to accrue to patients whose disease has progressed and/or to patients who no longer receive nivolumab. This was also observed in the assessment of nivolumab for lung cancer (non-small-cell, squamous, metastatic; ID811[49]). Moreover, in the appraisal consultation document of this assessment (issued October 2016), the committee concluded that *"the CheckMate-017 trial did not provide evidence for a dramatic gain in survival after disease progression with nivolumab compared with docetaxel"* and that *"some gain in survival after disease progression would be plausible and would be consistent with the mechanism of action of nivolumab; however, it concluded overall that the size of the gain implied by the company's model was neither plausible nor supported by the clinical-trial evidence"*.[77] However, it is unclear whether these statements based on the CheckMate 017 trial are also applicable to the present assessment, based on the CheckMate 141 trial. Given these uncertainties with regards to the post-progression benefits of nivolumab (i.e. long-term extrapolation), the ERG performed exploratory analyses using a shorter time horizon.

It should be noted that both the DSA and PSA performed by the company did not consider the uncertainty in the estimation of the OS, PFS and TTD (i.e. parameters for the time-to-event models were considered fixed). Therefore, the incremental cost effectiveness planes, reported in the CS, were not presented in the ERG report as the uncertainty presented in these plots is very likely to be underestimated. Moreover, the CEACs presented in the CS were not presented in the ERG report as these were three pairwise comparisons instead of all treatments simultaneously. The latter approach would be considered good practice by the ERG and was therefore requested (clarification question B13). The updated CEACs provided by the company considered all treatments simultaneously, incorporated treatment effectiveness parameters stochastically (though the correlation between the parameters was not incorporated) and showed that with the PAS, the probability that nivolumab is cost effective is 42% and 68% at thresholds of £30,000 and £50,000 per QALY respectively (Figure 5.8).[11]

The scenario analyses, provided by the company using treatment specific effectiveness parameters for OS, PFS and TTD resulted in similar ICERs compared with the company base-case and ranged from £33,756 to £34,286 for nivolumab with PAS (clarification in response to request for clarification, Table 22).[11]

In the ERG base-case (Section 5.3), the estimation of OS, PFS and TTD will be incorporated stochastically (as in the updated company base-case). Moreover, the standard deviation for utility values was incorrectly used in the PSA by the company; this will be corrected in the ERG base-case (using the standard error).

The equivalence assumptions between docetaxel and methotrexate as well as between docetaxel and paclitaxel can be questioned. Moreover, a scenario analysis, provided by the company (response to request for clarification letter Table 22),[11] using treatment specific effectiveness estimates for docetaxel and methotrexate (instead of using IC effectiveness), showed that the assumption of equivalence between docetaxel and methotrexate is not likely to be influential in terms of incremental QALYs, incremental costs and the ICER. To examine the assumption of equivalence between docetaxel and paclitaxel, the ERG performed a threshold analysis (conditional on the deterministic ERG base-case). This analysis indicated that if paclitaxel is more effective than docetaxel in terms of OS and PFS, up to a HR of approximately 0.93, nivolumab would not be cost effective compared with paclitaxel (assuming a threshold of £50,000 per QALY). Additionally, the cost effectiveness of nivolumab versus paclitaxel is uncertain given that, in Section 4.4, it is concluded there is some evidence, albeit weak, that paclitaxel is possibly more effective than nivolumab.

An additional area of uncertainty is the generalisability of the CheckMate 141 trial to UK clinical practice. This is questioned in Section 4 of this report, most particularly in terms of patient characteristics that would determine both intended treatment and prognosis. Section 4 concludes that despite that it seems plausible that nivolumab extends life expectancy, it is unclear by how much in comparison to docetaxel, paclitaxel and methotrexate. As the treatment effectiveness in the health economic model is primarily based on the CheckMate 141 trial, these reservations are also applicable to the estimated cost effectiveness, in particularly considering the magnitude of the post-progression benefits.

In conclusion, given the ERG base-case ICERs (with PAS) are estimated to be around £50,000 per QALY gained, the large uncertainty regarding extrapolation and post-progression benefits in combination with the lack of external validation of long-term outcomes and the doubt about the generalisability of the CheckMate 141 trial results to the UK the decision, uncertainty around the cost effectiveness of nivolumab remains substantial.

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

The company did seem to include all relevant controlled trials given that the inclusion criteria were broad enough not to exclude on the basis of design or any of the comparators. However, it appears that there is only one RCT that at least approximately matches the population in the scope i.e. CheckMate 141. Unfortunately, it lacks any comparison with one of the comparators defined in the NICE scope, i.e. paclitaxel. Also, it does have some significant limitations, including a comparison not with the comparators in the scope, but with IC, which permits clinician choice of treatment. This therefore means that the ITT analysis prevents an unbiased estimate of the effectiveness of nivolumab versus any of the comparators. It did, however, show a statistically significant advantage in OS versus IC, which might be considered an unbiased estimate versus standard care, but only if IC was made on the same basis as that in clinical practice. However, there is no way of knowing that and it would have to mean that precisely the same proportion of patients was eligible for each of the therapies (methotrexate, docetaxel and cetuximab) as in the trial. To compound the problem, one of the choices was cetuximab, which is not in the scope. Therefore, the ERG considers that the representativeness of the CheckMate 141 trial to clinical practice in the United Kingdom (UK) is highly questionable most particularly in terms of patient characteristics that would determine both intended treatment and prognosis.

The ERG did ask in the clarification letter for analyses to attempt to overcome these two main limitations, i.e. the inclusion of cetuximab and the missing comparison with paclitaxel. In response, the company did demonstrate little effect of the removal of the cetuximab patients, which was likely given the small number (n=15). They also provided three tables, which summarised the design, baseline characteristics and outcomes of five paclitaxel trials. The ERG concluded that, whilst there is no direct or indirect comparison of paclitaxel to either nivolumab or any of the IC treatments in CheckMate 141 and comparability is difficult to establish, there does seem to be some evidence, albeit weak, that paclitaxel is likely to be more effective than docetaxel and possibly more effective than nivolumab. Also, the response to a clarification question regarding the difference in the HRs for OS between the European Union and North America highlighted the difference in percentage receiving each of the treatments in the scope (docetaxel and methotrexate). The ERG would therefore conclude that, whilst it is reasonable to believe that nivolumab extends life expectancy, it is impossible to be confident by how much in comparison to any treatment in the scope or which is considered to be standard care in the UK.

The company base-case ICERs (probabilistic) of nivolumab (with PAS) compared with docetaxel, paclitaxel and methotrexate were £35,157, £35,025 and £35,091 respectively. The ERG has incorporated various adjustments to the company base-case. The ERG base-case resulted in ICERs (probabilistic) of £49,848, £46,611 and £46,565 for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate respectively. The most influential adjustments/corrections made by the ERG were 1) using a generalised-gamma distribution for estimating TTD; 2) using treatment independent utilities for PFS and PD health state utility values and; 3) using a dose and frequency of administration for docetaxel (75 mg/m2 Q3W) consistent with UK clinical practice. Moreover, in an exploratory analysis, the ERG used an adjusted dosage for nivolumab (fixed dose of 240 mg every two weeks) that was recently recommended by the FDA for renal-cell carcinoma, metastatic melanoma, and non-small cell lung cancer. This exploratory analysis, which was performed conditional upon the ERG base-case, resulted in ICERs (with PAS) of £50,160 - £53,439. Moreover, applying shorter time horizons, to explore the impact of the extrapolating estimated benefits of costs,

resulted in increased ICERs versus nivolumab to £91,687 to £98,925 (two year) and £59,984 to £63,833 (five year).

The equivalence assumptions between docetaxel and methotrexate as well as between docetaxel and paclitaxel can be questioned. However, a scenario analysis, provided by the company, using treatment specific effectiveness estimates for docetaxel and methotrexate (instead of using IC effectiveness), showed that the assumption of equivalence between docetaxel and methotrexate is not likely to be influential in terms of incremental QALYs, incremental costs and the ICER. To examine the assumption of equivalence between docetaxel and paclitaxel, the ERG performed a threshold analysis (conditional on the deterministic ERG base-case). This analysis indicated that if paclitaxel is more effective than docetaxel in terms of OS and PFS, up to a HR of approximately 0.93, nivolumab would not be cost effective compared with paclitaxel (assuming a threshold of £50,000 per QALY). Additionally, the cost effectiveness of nivolumab versus paclitaxel is uncertain given that, in Section 4.4, it is concluded there is some evidence, albeit weak, that paclitaxel is possibly more effective than nivolumab.

In conclusion, given the ERG base-case ICERs (with PAS) are estimated to be around £50,000 per QALY gained, the large uncertainty regarding extrapolation and post-progression benefits in combination with the lack of external validation of long-term outcomes and the doubt about the generalisability of the CheckMate 141 trial results to the UK the decision, uncertainty around the cost effectiveness of nivolumab remains substantial.

8.2 Strengths and limitations of the assessment

The searches in the CS were well documented and easily reproducible; searches were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[84] Significant differences were noted between the original clinical effectiveness strategy and that used for the 2015 update. The MEDLINE and Embase searches were limited to English language only, which may have introduced a language bias. Separate adverse events searches were not conducted.

The ERG identified two issues which might limit the generalisability of results of the CheckMate 141 trial.

1. Based on information in the CS and the response for request for clarification, the prevalence of males in the index population is approximately 70%. It should be noted that 83.1% of the trial population is male. Given that discrepant results are reported for OS (nivolumab versus IC; HR 0.65 (95% CI 0.48 to 0.88) and 0.93 (95% CI 0.47 to 1.85) for males and females, respectively), this issue might influence the applicability of study results to the overall UK population.
2. The ERG noticed differences in the OS HRs between participants from North America and the European Union (EU), i.e. 0.55 (95% CI 0.36 to 0.85) and 0.91 (95% CI 0.62 to 1.33), respectively. In response to request for clarification, the company offered several explanations, including the lower proportion of human papillomavirus (HPV)-positive and never smoker patients in Europe, an imbalance of HPV status across treatment arms within the European subgroup and differences in choice of IC of therapy. Differences in the recorded baseline characteristics between the EU and North America as well as in the treatments chosen highlights the potential for lack of applicability to the UK.

The economic model structure is similar to other oncology assessments, similar to previous nivolumab appraisals and seems appropriate for the current decision problem. Moreover, the ERG considered the statistical methods used by the company for selecting the distributions for the time-to

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3rd February 2017

Re: Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy [ID971] – request for additional evidence

Dear Helen,

Bristol-Myers Squibb (BMS) Pharmaceuticals Limited welcome the opportunity to provide further evidence in response to a request from NICE to support the case for nivolumab as a cost-effectiveness use of NHS resources for patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) after platinum-based therapy, ahead of a second Committee meeting.

Please find herewith results from the revised base case analysis with details provided as to how each of the requests from NICE have been addressed.

Yours sincerely,

[redacted]

[redacted]

1.1 The committee recommends that NICE requests the following further information from the company for the second appraisal committee meeting:

Response 1

- updated clinical-effectiveness data from the latest data-cut of the CheckMate-141 trial

An overview of the clinical effectiveness results from the latest database lock of the CheckMate 141 trial (20th September 2016) are presented in Table 1. Further details on each of these outcomes are presented in subsequent sections. The corresponding results from the initial database locks are presented in Table 15 of the original Company Evidence Submission (reproduced in Appendix 1 here).

Table 1: Overview of clinical effectiveness results from the latest database lock of CheckMate 141 (20th September 2016) – all-randomised population

Outcome	Nivolumab (n=240)	IC (n=121)
Overall survival		
Deaths	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR for death with nivolumab (95% CI; p-value)	[redacted]	
18-month survival rate, % (95% CI)	[redacted]	[redacted]
24-month survival rate, % (95% CI)	[redacted]	[redacted]
Progression-free survival[a]		
Events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
HR for progression or death with nivolumab (95% CI; p-value)	[redacted]	
18-month PFS rate, % (95% CI)	[redacted]	[redacted]
24-month PFS rate, % (95% CI)	[redacted]	[redacted]
Tumour response[a]		
ORR, n (%)[b] [95% CI]	[redacted]	[redacted]
Median TTR, months (range)	[redacted]	[redacted]
Median DOR, months (range)	[redacted]	[redacted]

[a] Disease progression and tumour response were assessed by the investigator using RECIST version 1.1.
[b] ORR was defined as the number of responders (partial or complete) as a proportion of the total number of patients in each treatment arm.

Abbreviations: CI: confidence intervals; DOR: duration of response; HR: hazard ratio; NR: not reached; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumours; TTR: time to response.
Source: CheckMate 141 CSR Addendum (17th November 2016).[1]

Overall survival (OS)

At the latest database lock (20th September 2016), deaths had occurred in [redacted]% and [redacted]% of patients in the nivolumab and investigator's choice (IC) arms, respectively, and the median duration of follow-up for OS was [redacted] months in the nivolumab arm and [redacted] months in the IC arm.[1] Median OS in both arms ([redacted] months in the nivolumab arm and [redacted] months in the IC arm), [redacted]; latest database lock) (see Table 1 compared to Appendix 1).[1] The Kaplan-Meier plot for OS from the latest database lock is presented in Figure 1.

Progression-free survival (PFS)

At the time of the latest database lock (20th September 2016), an additional [redacted] PFS event in the IC arm ([redacted]% of patients in total) and [redacted] PFS events in the nivolumab arm ([redacted]% of patients in total) had occurred since the initial database lock.[1] [redacted]; latest database lock) (see Figure 2 for the Kaplan-Meier plot).[1]

Tumour response – Objective Response Rate (ORR), Time to Response (TTR) and Duration of Response (DOR)

At the time of the latest database lock (20th September 2016), the ORR and median TTR [redacted] from that reported at the initial database lock.[1] Median DOR, which was not analysed at the earlier cut-off date, was higher in the nivolumab arm ([redacted] months; 95% CI, [redacted]), than in the IC arm ([redacted] months; 95% CI [redacted]), supporting a trend for a more durable response with nivolumab compared IC of therapy.[1] A summary of tumour response data from the latest database lock is presented in Table 2.

Table 2: Response to treatment at the latest database lock of CheckMate 141 (20th September 2016) – all-randomised population

Tumour response	Nivolumab (n=240)	IC (n=121)
Best overall response, n (%)		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not determined	[redacted]	[redacted]
ORR, n (%) [95% CI]	[redacted]	[redacted]
Median TTR, months (range)	[redacted]	[redacted]
Median DOR, months (95% CI)	[redacted]	[redacted]

Response was assessed by the investigator using RECIST version 1.1.

Abbreviations: CI: confidence intervals; DOR: duration of response; IC: investigator's choice; NR: not reached; ORR: objective response rate; RECIST: Response Evaluation Criteria In Solid Tumours; TTR: time to response.
Source: CheckMate 141 CSR Addendum (17th November 2016) – Table 6.3-1.[1]

Figure 1: Kaplan-Meier plot for overall survival at the latest database lock of CheckMate 141 (20th September 2016) – all-randomised population

Abbreviations: CI: confidence interval; INV Choice: investigator's choice; NIVO: nivolumab.
Source: CheckMate 141 CSR Addendum (17th November 2016) – Figure 6.1-1.[1]

Figure 2: Kaplan-Meier plot for progression-free survival at the latest database lock of CheckMate 141 (20th September 2016) – all-randomised population

Abbreviations: CI: confidence interval; INV Choice: investigator's choice; NIVO: nivolumab.
Source: CheckMate 141 CSR Addendum (17th November 2016) – Figure 6.2-1.[1]

Time on therapy and subsequent therapies

At the latest database lock (20th September 2016), [redacted] 3[redacted].[2]

Subsequent systemic anticancer therapies were received by [redacted] ([redacted]% in the nivolumab arm and [redacted]% in the IC arm), but with a [redacted] in the IC arm ([redacted]%) receiving treatment with subsequent therapy with immunotherapies (including nivolumab) compared to the nivolumab arm ([redacted]%) (not including [redacted]) (see Table 3).[1, 3]

Figure 3: Kaplan-Meier plot of duration of therapy in the all-treated population at the latest database lock of CheckMate 141 (20th September 2016)

Abbreviations: CI: confidence interval; INV Choice: investigator's choice; NIVO: nivolumab.
Source: CheckMate 141 CSR Addendum (17th November 2016) – Figure 5.1-1[1]

Table 3: Subsequent immunotherapy treatment that had been received in CheckMate 141 at the latest database lock of CheckMate 141 (20th September 2016)

Subsequent therapy, n (%)	Nivolumab (n=240)	IC (n=121)
Any systemic therapy	[redacted]	[redacted]
Immunotherapy		
Investigational drug immunotherapy	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Urelumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Crossover to nivolumab	[redacted]	[redacted]

Abbreviations: IC: investigator's choice.
Source: CheckMate 141 CSR Addendum (17th November 2016) – Table 5.4-1[1] and CheckMate 141: Data on File.[3]

Response 2

- a revised base-case cost-effectiveness analysis for nivolumab compared with docetaxel, paclitaxel and methotrexate that:
  - includes the latest data from CheckMate-141
  - uses the Kaplan–Meier data from CheckMate-141 for the earlier phase of the model followed by appropriate parametric curves to extrapolate to the remainder of the model time horizon for all outcomes
  - re-analyse utility data using robust methods to estimate the treatment-dependent health-state utility values, appropriately adjusting for missing data
  - incorporates the recommended dosing regimen for docetaxel used in clinical practice in England (75 mg/m^2, once every 3 weeks)

Cost-effectiveness results for pairwise comparisons of nivolumab versus docetaxel, paclitaxel and methotrexate are presented in Table 4 (without PAS for nivolumab) and Table 5 (with PAS for nivolumab) from a revised base case analysis that BMS believes provides the most plausible estimates of cost effectiveness for nivolumab versus each of the relevant comparators.

Table 4: Deterministic base case results (without PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Base case: 25% of patients who are still receiving nivolumab at 2 years remain on treatment							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
50% of patients who are still receiving nivolumab at 2 years remain on treatment							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
75% of patients who are still receiving nivolumab at 2 years remain on treatment							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 5: Deterministic base case results (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Base case: 25% of patients who are still receiving nivolumab at 2 years remain on treatment							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	£44,636
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	£41,240
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	£42,079
50% of patients who are still receiving nivolumab at 2 years remain on treatment							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	£45,453
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	£42,057
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	£42,895
75% of patients who are still receiving nivolumab at 2 years remain on treatment							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	£46,270
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	£42,873
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	£43,712

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

This revised base case analysis for which results are presented above includes the following changes to that presented in the original Company Evidence Submission:

- Uses Kaplan-Meier survival data for OS, PFS and time to discontinuation (TTD) from the latest database lock (20th September 2016)
- Uses treatment-arm specific health-state utility values based on results of a mixed model regression analysis
- Uses a dosing regimen of 75 mg/m^2, once every 3 weeks, for calculating docetaxel drug acquisition costs

In addition, the revised base case analysis includes the application of a 2-year clinical stopping rule for nivolumab. To implement this stopping rule in the model, a proportion of patients who were still receiving nivolumab after two years according to the extrapolated TTD curve were modelled to remain on treatment with nivolumab, with all other parameters remaining the same. In the base case the proportion used was 25%; the impact of altering the proportion assumed to remain on treatment after two years to 50% and 75% was also explored. Cost-effectiveness results are also presented in Table 6 (without PAS for nivolumab) and Table 7 (with PAS for nivolumab) for a scenario in which no clinical stopping rule is applied.

Table 6: Scenario results (without PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 7: Scenario results (with PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	£47,086
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	£43,690
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	£44,528

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

As in the original Company Evidence Submission, parametric distributions to extrapolate survival across the entirety of the time horizon, based on the full set of Kaplan-Meier data from the latest database lock of CheckMate 141, have been used to model OS, PFS and TTD. As per the original Company Evidence Submission, the same curve choice was applied to both the nivolumab and IC arm.

In light of the availability of survival data from the latest database lock of CheckMate 141, the choice of parametric curves for the revised base case analysis has been revisited. For OS and PFS the choice of curves remains the same as those selected in the original Company Evidence Submission (lognormal for OS and generalised-gamma for PFS). For TTD, the generalised-gamma distribution was selected as the best-fitting non-spline model that did not produce any logical inconsistencies in either treatment arm (i.e., it did not predict a greater proportion of patients on treatment than were alive in a given cycle). This was also the distribution preferred by the Evidence Review Group (ERG) for modelling TTD following their review of the original Company Evidence Submission. Further details on the choice of curves for the revised base case analysis are presented in Appendix 2. Piecewise survival analyses have been explored, as requested (and are included in the revised model for transparency), but it is the opinion of BMS that these models, when using an exponential distribution for extrapolation, severely underestimate long-term survival with nivolumab given the durable survival benefits that have been seen in other indications for which data from longer-term follow-up are available.[4-6] There is both a clear biological rationale and now an increasing evidence base of long-term data to support the case for a prolonged survival benefit for some patients with nivolumab. These piecewise survival analyses have therefore not been used for the revised base case analysis.

The justifications for these model choices are discussed in more detail below.

Extrapolation of survival

Extrapolation across the entirety of the time horizon using all Kaplan-Meier data

The approach of using parametric survival curves to extrapolate survival over the entire time horizon using the full set of Kaplan-Meier data from the latest database lock of CheckMate 141 has been adopted for the revised base case analysis, as per the original Company Evidence Submission. This approach is consistent with guidance from the NICE Decision Support Unit (DSU) and the selection of curves was considered to be appropriate by the ERG in their assessment of the original Company Evidence Submission: "*the ERG considered the statistical methods used by the company for selecting the distributions for the time-to event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis*."[7]

The parametric distributions selected for the revised base case analysis were as follows (see Appendix 2 for full details):

- Lognormal for OS
- Generalised-gamma for PFS
- Generalised-gamma for TTD

As in the original Company Evidence Submission, the survival rates predicted by the parametric curves selected for the revised base case analysis have been validated against appropriate sources of available evidence. This constituted of clinical expert opinion for IC and long-term data from nivolumab trials in advanced squamous non-small cell lung cancer (NSCLC), including CheckMate 003, which looked at patients who had progressed after platinum- or taxane-based therapy.[8] As described in the original Company Evidence Submission, squamous NSCLC was identified by clinical experts as being the most relevant in terms of the similarity between indications in terms of tumour histology, patient characteristics (e.g., age and smoking status) and prognosis.[9]

For IC, the survival estimates predicted by the revised base case model are broadly consistent with the expectations of clinical experts for patients receiving currently-available therapies in clinical practice (see Table 8). The higher survival rates predicted by the model at two years compared to clinician expectations may be due to the use of PD-L1 inhibitors (including nivolumab) and other immunotherapies as post-discontinuation therapies in the IC arm of CheckMate 141 (see Table 3 in Response 1). The cost-effectiveness analyses presented here have not been adjusted for post-discontinuation therapies or crossover. To explore the implications of this, a scenario in which survival outcomes for the IC arm are modelled using an alternative survival distribution to the one chosen for nivolumab has also been conducted (see 'piecewise model scenario 2' as part of this response). This is an attempt to accurately characterise the current OS range estimated by clinical experts and to explore the possibility that patients on current standard of care (i.e., single-agent chemotherapy) have a different shaped survival function than patients receiving nivolumab.

For nivolumab, 5-year survival data from the CheckMate 003 trial have become available (database lock of 15th November 2016) since the original Company Evidence Submission for ID971, which has allowed for further validation of the modelled survival for nivolumab in the longer term. In support of the long-term survival predicted by the lognormal curve choice for R/M SCCHN patients receiving nivolumab, survival data from the latest database lock of CheckMate

003 [redacted] (see Figure 4). Looking at absolute survival estimates, specifically, the lognormal curve used in the revised base case analysis provided estimates of OS up to five years that are [redacted] (see Table 8).

Table 8: Validation of absolute OS estimates for nivolumab and IC predicted by the revised base case analysis

Data source	Survival curve	Proportion alive, %					
		1 year	1.5 years	2 years	3 years	4 years	5 years
IC							
Model estimates for OS	Lognormal (Base case)	19.2%	9.5%	5.7%	2.3%	1.1%	0.6%
CheckMate 141	Nivolumab OS	[redacted]	[redacted]	[redacted]	-	-	-
Clinical expert opinion	-	10–20%	-	≤5%	-	1%	-
Nivolumab							
Model estimates for OS	Lognormal	32.9%	22.0%	16.5%	10.0%	6.7%	4.7%
CheckMate 141 (R/M SCCHN)	Nivolumab OS	[redacted]	[redacted]	[redacted]	-	-	-
CheckMate 003 (squamous NSCLC) – *absolute*	Nivolumab OS	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]

CheckMate 003 = dose-ranging phase I trial of nivolumab in multiple tumour types, including patients with advanced, squamous NSCLC treated with nivolumab 1, 3 or 10 mg/kg, once every two weeks (n=54), until 96 weeks.[8]

Abbreviations: IC: investigator's choice; NSCLC: non-small cell lung cancer; OS: overall survival; R/M: recurrent or metastatic; SCCHN: squamous cell carcinoma of the head and neck.
Source: CheckMate 141 CSR Addendum (17th November 2016)[1] and CheckMate 003 (database lock: 15th November 2016). Data on File.[5] Expert clinical opinion.[9, 10]

Figure 4: Kaplan-Meier plot for overall survival at the latest database lock of CheckMate 003 (15th November 2016) – all-treated population; previously-treated squamous cell carcinoma patients

Source: CheckMate 003 (database lock: 15th November 2016). Data on File.[5]

As noted in the original Company Evidence Submission, there are limitations in assuming that absolute survival estimates are comparable across different indications. An analysis has therefore also been conducted to consider the conditional year-on-year estimates of survival with nivolumab from the long-term data from CheckMate 003. These conditional estimates may be a more useful comparison than absolute estimates as they take into account the potential inherent differences in absolute survival between different indications. The conditional survival estimates for CheckMate 003 are presented in Table 9 alongside those predicted by the lognormal curve used for the revised base case analysis. This indicates that the lognormal OS curve for nivolumab in the revised base case model predicts [redacted] than has been observed with nivolumab as a treatment for previously-treated squamous NSCLC.

Table 9: Conditional year-on-year OS estimates for nivolumab predicted by the revised base case analysis

Data source	Survival curve	Proportion alive, %				
		1 year	2 years	3 years	4 years	5 years
Model estimates for OS	Lognormal	32.9%	50.2%	60.6%	67.0%	70.1%
CheckMate 141 (R/M SCCHN)	Nivolumab OS	[redacted]	[redacted]	-	-	-
CheckMate 003 (squamous NSCLC) - *conditional*	Nivolumab OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival.

In Figure 5 the conditional survival estimates from CheckMate 003 have been applied to the 2-year absolute survival estimates reported in CheckMate 141. This analysis makes use of the Kaplan-Meier data from the indication of R/M SCCHN specifically up to the time point for which this data is available in the CheckMate 141 study (i.e., two years) and then extrapolates survival from this point based on observed longer-term conditional survival rates from the CheckMate 003 trial. In this analysis, [redacted] compared to the application of conditional estimates of survival from CheckMate 003 to CheckMate 141 absolute estimates from Year 2 onwards (see Figure 5).

Figure 5: Comparison of lognormal survival estimates with conditional survival-based extrapolations from CheckMate 003

[redacted]

The validation exercises presented above show that the OS estimates predicted from the revised base case analysis, using extrapolation based on the full set of Kaplan-Meier data, are generally consistent with those expected by clinical experts for IC and [redacted] relative to observed survival in squamous NSCLC trials which have longer follow-up than CheckMate 141. BMS therefore believe that the extrapolation of survival based on the full set of Kaplan-Meier data, using curves selected according to guidance from the NICE DSU, is both valid and appropriate and this approach has therefore been presented to the Committee as the preferred approach for the base case analysis.

Piecewise approach to extrapolation

Although BMS consider it inappropriate to inform the revised base case analysis, the use of Kaplan-Meier survival data up to a specified time point in the model, followed by the use of an appropriate parametric curve to extrapolate survival from this cut-off point to the end of the time horizon (piecewise approach), has been explored in order to address the request made by NICE.

In these piecewise analyses, survival in the first phase was determined by the Kaplan-Meier survival data from the latest database lock of CheckMate 141. For the second phase, survival was modelled using parametric distributions fitted to the subset of patients who were still at risk at the chosen cut-off point. The survival function for this second phase was then adjusted in order to convey survival from the start of the trial and thus generate the two-phase survival curve.

The exponential distribution was chosen to model OS for the second phase of the piecewise survival analyses given the Committee's preference for the analysis to replicate the piecewise survival models previously submitted to NICE for another PD-L1 inhibitor (pembrolizumab for PD-L1 positive NSCLC after chemotherapy [TA428]).[11] The choice of cut-off point for extrapolation was based on inspection of the log cumulative hazards plot for nivolumab and IC (see Figure 6), with time points of 20, 28, 36 and 48 weeks selected to explore multiple cut-off points. Multiples of four weeks were used in order to fit with the cycle length used in the cost-effectiveness model. Cut-off points beyond 48 weeks were not explored as the number of patients at risk in the IC group after one year was considered to be too low.

Ultimately, the selection of a cut-off time point is a balance between making maximal use of the available Kaplan-Meier data directly (i.e., choosing a later cut-off) versus ensuring sufficient patient numbers to allow appropriate fitting of a parametric distribution (i.e., choosing an earlier cut-off). The earlier the cut-off point used, the more the piecewise analysis tends to the usual approach of fitting a parametric distribution to the full set of Kaplan-Meier data across the entire time horizon. It should be noted that the exponential was not considered to be a good fit to the full set of Kaplan-Meier data when choosing the most appropriate fully parametric curve (see Appendix 2), highlighting further the inappropriateness of fitting an exponential distribution to the nivolumab arm based on the latest data from CheckMate-141.

Figure 6: Log cumulative hazard plot for overall survival with cut-off points for piecewise survival analysis

The extrapolations of OS with nivolumab up to five years for each of these piecewise analyses are presented in Figure 7 alongside the lognormal distribution that is preferred for the revised base case analysis and the extrapolated survival based on conditional year-on-year survival from CheckMate 003. Absolute survival estimates from these analyses are presented in Table 10. In each piecewise extrapolation using the exponential distribution, compared to the extrapolation using conditional survival estimates from CheckMate 003 (see Figure 7 and Table 10), and none of these exponential piecewise analyses allowed for the possibility of a plateau in the survival curve for nivolumab that has been observed consistently in other indications.[4-6] These models are not therefore considered appropriate for the extrapolation of long-term survival with nivolumab as they do not accurately reflect the durable survival benefits that nivolumab, as an immune-checkpoint inhibitor, can potentially offer some patients. Piecewise models using an exponential extrapolation were therefore not considered further with regards to nivolumab. Survival estimates from the piecewise analyses using the exponential distribution were however considered to be reasonable for the IC arm (albeit slightly pessimistic in the long term), as compared to the expectations of clinical experts with regards to the survival of patients receiving these therapies in clinical practice (see Table 11).

The limitations of the piecewise approach to modelling survival compared to fitting parametric distributions to the full Kaplan-Meier data have been published previously.[12, 13] Specifically, the need to select an appropriate cut-off point and the issues associated with fitting curves to the latter part of the Kaplan-Meier data, where the numbers at risk are vastly reduced, have been highlighted as key concerns.[12] Using trial data of ipilimumab as a treatment for advanced melanoma as an example, it was noted that, "*the selection of a suitable point on the Kaplan-Meier function from which to extrapolate becomes increasingly arbitrary as the effective sample size decreases*," and that, "*estimating survival based on parametric functions over the entire period in this case avoids the bias that might arise in extrapolating beyond the last observation point by appending parametric functions to a point in the tail of the Kaplan-Meier functions*."[13]

Figure 7: Overall survival extrapolations up to five years for exponential piecewise models compared to the lognormal extrapolation and conditional survival-based extrapolations from CheckMate 003

Abbreviations: KM: Kaplan-Meier.

Table 10: Absolute OS estimates for nivolumab predicted by the exponential piecewise models

Survival curve	Cut-off point (weeks)	Proportion alive, %				
		1 year	2 years	3 years	4 years	5 years
Piecewise (exponential)	20	34.4%	13.0%	4.9%	1.9%	0.7%
	28	34.7%	12.3%	4.3%	1.5%	0.5%
	36	33.9%	13.3%	5.2%	2.0%	0.8%
	48	33.1%	14.1%	6.0%	2.6%	1.1%
Base case (log-normal)	-	32.9%	16.5%	10.0%	6.7%	4.7%
CheckMate 141 plus CheckMate 003 from Year 3	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival.

Table 11: Absolute OS estimates for IC predicted by the exponential piecewise models

Source/ survival curve	Cut-off point (weeks)	Proportion alive, %				
		1 year	1.5 years	2 years	3 years	4 years
Piecewise (exponential)	20	19.4%	8.1%	3.8%	0.7%	0.1%
	28	19.5%	8.6%	4.2%	0.9%	0.2%
	36	19.7%	8.5%	4.1%	0.9%	0.2%
	48	18.0%	9.7%	5.7%	1.8%	0.6%
Base case (log-normal)	-	19.2%	9.5%	5.7%	2.3%	1.1%
CheckMate 141	-	[redacted]	[redacted]	[redacted]	-	-
Clinical expert opinion	-	10–20%	-	≤5%	-	1%

Abbreviations: IC: investigator's choice; OS: overall survival.
Source: CheckMate 141 CSR Addendum (17th November 2016)[1] and expert clinical opinion.[9, 10]

[redacted].[14, 15] In both appraisals, the use of piecewise survival analyses (as favoured by the ERG in these appraisals), which used an exponential distribution to extrapolate from the Kaplan-Meier curve, led to [redacted] (see Figure 8 for ID811, squamous NSCLC and Figure 9 for ID900, non-squamous NSCLC). The survival estimates from the BMS-preferred approach were [redacted].

Figure 8: Overall survival curve options presented as part of ID811 (squamous NSCLC)

BMS = BMS-preferred choice of survival curve, Intermediary = alternative survival curve that lay between BMS and ERG preferred choices and for which logical inconsistencies were avoided; ERG = piecewise survival model (exponential).

Abbreviations: BMS: Bristol-Myers Squibb; ERG: Evidence Review Group; NSCLC: non-small cell lung cancer.

Figure 9: Overall survival curve options presented as part of ID900 (non-squamous NSCLC)

BMS = BMS-preferred choice of survival curve, Intermediary = alternative survival curve that lay between BMS and ERG preferred choices and for which logical inconsistencies were avoided; ERG = piecewise survival model (exponential).

Abbreviations: BMS: Bristol-Myers Squibb; ERG: Evidence Review Group; NSCLC: non-small cell lung cancer.

In this appraisal [ID971], BMS consider the lognormal distribution (extrapolated over the entirety of the time horizon based on the full set of Kaplan-Meier data) to be a more appropriate method of extrapolation as this better characterises the possibility that nivolumab in R/M SCCHN may offer similar long-term survival benefits to those that have already been observed in squamous NSCLC and other indications with trials of longer follow-up than CheckMate 141.[4-6]

With respect of the request to present the results of analyses using this piecewise approach, two scenarios are presented below that use these models and that BMS consider to produce more plausible cost-effectiveness results that are that are based on appropriate estimates of OS with nivolumab and IC, compared to those derived from the exponential piecewise analysis.

1. **Piecewise model scenario 1: piecewise model using the lognormal distribution for the second phase (for nivolumab and IC)**

As discussed above, the use of the exponential distribution is not believed to produce extrapolations of OS that accurately characterise the long-term survival that nivolumab has already demonstrated in other indications with trials of longer follow-up than CheckMate 141.[4-6] An alternative parametric distribution with which to extrapolate from the Kaplan-Meier curve in the second phase of the piecewise model was therefore explored.

The lognormal distribution, which was selected for the base case analysis, provided a statistical fit that was considered to be as reasonable as the exponential distribution for both nivolumab and IC when applied at cut-off points of 20 weeks, 36 weeks and 48 weeks (see Table 12) (the 28-week cut-off point was not explored), and produced estimates of OS that were [redacted] (see Table 13). Furthermore, logical inconsistencies in which OS fell

below either PFS or TTD (using the base case curve selections for PFS and TTD), were avoided when using the lognormal distribution in the piecewise model, which was not the case for the exponential distribution (OS fell below PFS at all cut-off points except 48 weeks for IC and fell below PFS and TTD for all cut-off points for nivolumab). A scenario analysis using the lognormal distribution for the second phase of the piecewise survival model was therefore conducted.

Table 12: Summary of goodness-of-fit data for IC and nivolumab OS piecewise models at different cut-off points

Survival curve	Cut-off point (weeks)	IC		Nivolumab	
		AIC	BIC	AIC	BIC
Exponential	20	439.12	441.27	948.65	951.64
Lognormal	20	440.27	444.56	953.35	959.33
Exponential	36	218.14	219.75	553.46	556.11
Lognormal	36	217.73	220.95	556.29	561.6
Exponential	48	98.13	99.22	329.06	331.45
Lognormal	48	97.18	99.36	326.58	331.35

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

Table 13: Absolute OS estimates for IC and nivolumab predicted by the lognormal piecewise models

Source/ survival curve	Cut-off point (weeks)	Proportion alive, %					
		1 year	1.5 years	2 years	3 years	4 years	5 years
IC							
Piecewise (lognormal)	20	18.6%	10.7%	7.5%	4.2%	2.6%	1.8%
	36	17.5%	10.1%	7.4%	4.5%	3.2%	2.4%
	48	18.8%	9.0%	5.5%	2.4%	1.3%	0.8%
Base case (log-normal)	-	19.2%	9.5%	5.7%	2.3%	1.1%	0.6%
CheckMate 141	-	[redacted]	[redacted]	[redacted]	-	-	-
Clinical expert opinion	-	10–20%	-	≤5%	-	1%	-
Nivolumab							
Piecewise (lognormal)	20	32.7%	21.9%	16.7%	10.5%	7.3%	5.4%
	36	31.9%	21.3%	16.6%	11.2%	8.3%	6.5%
	48	34.1%	20.3%	14.1%	7.8%	5.0%	3.4%
Base case (log-normal)	-	32.9%	22.0%	16.5%	10.0%	6.7%	4.7%
CheckMate 141 plus CheckMate 003 from Year 3	-	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IC: investigator's choice; OS: overall survival.
Source: CheckMate 141 CSR Addendum (17th November 2016)[1] and CheckMate 003 (database lock: 15th November 2016). Data on File.[5] Expert clinical opinion.[9, 10]

The cost-effectiveness results from this piecewise scenario analysis, from each cut-off point, are presented in Table 14 (without PAS for nivolumab) and Table 15 (with PAS for nivolumab). All

other model settings for this scenario analysis were as per the revised base case analysis, including the application of a clinical stopping rule that assumed that 25% of patients who are still receiving nivolumab at two years remain on treatment. Table 16 (without PAS for nivolumab) and Table 17 (with PAS for nivolumab) present the results of the same scenario analysis with no clinical stopping rule applied.

Table 14: Piecewise model scenario 1 results (without PAS for nivolumab) – 25% of patients who are still receiving nivolumab at 2 years remain on treatment

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.26	[redacted]				
Docetaxel	10,682	0.77	0.41	[redacted]	0.49	[redacted]	[redacted]
Paclitaxel	12,081	0.77	0.41	[redacted]	0.49	[redacted]	[redacted]
Methotrexate	11,736	0.77	0.41	[redacted]	0.49	[redacted]	[redacted]
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.37	[redacted]				
Docetaxel	10,777	0.82	0.43	[redacted]	0.55	[redacted]	[redacted]
Paclitaxel	12,176	0.82	0.43	[redacted]	0.55	[redacted]	[redacted]
Methotrexate	11,831	0.82	0.43	[redacted]	0.55	[redacted]	[redacted]
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.10	[redacted]				
Docetaxel	10,499	0.68	0.37	[redacted]	0.41	[redacted]	[redacted]
Paclitaxel	11,899	0.68	0.37	[redacted]	0.41	[redacted]	[redacted]
Methotrexate	11,553	0.68	0.37	[redacted]	0.41	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 15: Piecewise model scenario 1 results (with PAS for nivolumab) – 25% of patients who are still receiving nivolumab at 2 years remain on treatment

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.26	[redacted]				
Docetaxel	10,682	0.77	0.41	[redacted]	0.49	[redacted]	£45,008
Paclitaxel	12,081	0.77	0.41	[redacted]	0.49	[redacted]	£41,571
Methotrexate	11,736	0.77	0.41	[redacted]	0.49	[redacted]	£42,420
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.37	[redacted]				
Docetaxel	10,777	0.82	0.43	[redacted]	0.55	[redacted]	£40,781
Paclitaxel	12,176	0.82	0.43	[redacted]	0.55	[redacted]	£37,686
Methotrexate	11,831	0.82	0.43	[redacted]	0.55	[redacted]	£38,450
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.10	[redacted]				
Docetaxel	10,499	0.68	0.37	[redacted]	0.41	[redacted]	£52,675
Paclitaxel	11,899	0.68	0.37	[redacted]	0.41	[redacted]	£48,617
Methotrexate	11,553	0.68	0.37	[redacted]	0.41	[redacted]	£49,619

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 16: Piecewise model scenario 1 results (without PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.26	[redacted]				
Docetaxel	10,682	0.77	0.41	[redacted]	0.49	[redacted]	[redacted]
Paclitaxel	12,081	0.77	0.41	[redacted]	0.49	[redacted]	[redacted]
Methotrexate	11,736	0.77	0.41	[redacted]	0.49	[redacted]	[redacted]
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.37	[redacted]				
Docetaxel	10,777	0.82	0.43	[redacted]	0.55	[redacted]	[redacted]
Paclitaxel	12,176	0.82	0.43	[redacted]	0.55	[redacted]	[redacted]
Methotrexate	11,831	0.82	0.43	[redacted]	0.55	[redacted]	[redacted]
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.10	[redacted]				
Docetaxel	10,499	0.68	0.37	[redacted]	0.41	[redacted]	[redacted]
Paclitaxel	11,899	0.68	0.37	[redacted]	0.41	[redacted]	[redacted]
Methotrexate	11,553	0.68	0.37	[redacted]	0.41	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 17: Piecewise model scenario 1 results (with PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.26	[redacted]				
Docetaxel	10,682	0.77	0.41	[redacted]	0.49	[redacted]	£47,487
Paclitaxel	12,081	0.77	0.41	[redacted]	0.49	[redacted]	£44,050
Methotrexate	11,736	0.77	0.41	[redacted]	0.49	[redacted]	£44,899
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.37	[redacted]				
Docetaxel	10,777	0.82	0.43	[redacted]	0.55	[redacted]	£43,013
Paclitaxel	12,176	0.82	0.43	[redacted]	0.55	[redacted]	£39,918
Methotrexate	11,831	0.82	0.43	[redacted]	0.55	[redacted]	£40,682
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.10	[redacted]				
Docetaxel	10,499	0.68	0.37	[redacted]	0.41	[redacted]	£55,602
Paclitaxel	11,899	0.68	0.37	[redacted]	0.41	[redacted]	£51,544
Methotrexate	11,553	0.68	0.37	[redacted]	0.41	[redacted]	£52,546

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

2. Piecewise model scenario 2: piecewise model using the exponential distribution for the second phase (for IC only) and the lognormal distribution over the entire time horizon based on the full set of Kaplan-Meier data (for nivolumab)

As shown in Table 11, the piecewise model using the exponential distribution provided reasonable estimates of survival in the IC arm. These survival estimates were slightly lower than those predicted by the lognormal distribution in the base case analysis and are at the more pessimistic end of clinician expectations of survival with these therapies (see Table 11). An analysis using the exponential distribution as part of piecewise analyses for the IC arm was therefore conducted in order to examine the impact on the cost-effectiveness results if a pessimistic survival curve for IC was selected. The purpose of this analysis was to explore (indirectly) the possibility that survival in the IC arm, as reported in the latest database lock, was confounded by the higher proportion of patients in the IC arm receiving subsequent immunotherapies (or crossing over to nivolumab), compared to the nivolumab arm (see Table 3 in Response 1).

For the extrapolation of OS for nivolumab, the piecewise model using the exponential distribution was not considered to be appropriate for this scenario analysis, for the reasons outlined above. Although there is generally a preference for both treatment arms to use the same curve selection, it was considered reasonable to depart from this for this scenario analysis given the fact that the piecewise model using the exponential distribution has been shown to be inappropriate for modelling survival with nivolumab, and also to consider the possibility that nivolumab, as an immune checkpoint inhibitor, has a distinct survival function to chemotherapy. For this scenario, the base case approach (lognormal across the entirety of the time horizon, based on the full set of Kaplan-Meier data), has therefore been used to model OS for nivolumab.

The cost-effectiveness results from this piecewise scenario analysis, from each cut-off point, are presented in Table 18 (without PAS for nivolumab) and Table 19 (with PAS for nivolumab). All other model settings for this scenario analysis were as per the revised base case analysis, including the application of a clinical stopping rule that assumed that 25% of patients who are still receiving nivolumab at two years remain on treatment. Table 20 (without PAS for nivolumab) and Table 21 (with PAS for nivolumab) present the results of the same scenario analysis with no clinical stopping rule applied.

Table 18: Piecewise model scenario 2 results (without PAS for nivolumab) – 25% of patients who are still receiving nivolumab at 2 years remain on treatment

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,381	0.63	0.34	[redacted]	0.57	[redacted]	[redacted]
Paclitaxel	11,780	0.63	0.34	[redacted]	0.57	[redacted]	[redacted]
Methotrexate	11,435	0.63	0.34	[redacted]	0.57	[redacted]	[redacted]
Cut-off point: 28 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,389	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Paclitaxel	11,788	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Methotrexate	11,443	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,388	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Paclitaxel	11,787	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Methotrexate	11,442	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,436	0.65	0.35	[redacted]	0.54	[redacted]	[redacted]
Paclitaxel	11,836	0.65	0.35	[redacted]	0.54	[redacted]	[redacted]
Methotrexate	11,490	0.65	0.35	[redacted]	0.54	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 19: Piecewise model scenario 2 results (with PAS for nivolumab) – 25% of patients who are still receiving nivolumab at 2 years remain on treatment

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,381	0.63	0.34	[redacted]	0.57	[redacted]	£42,503
Paclitaxel	11,780	0.63	0.34	[redacted]	0.57	[redacted]	£39,287
Methotrexate	11,435	0.63	0.34	[redacted]	0.57	[redacted]	£40,081
Cut-off point: 28 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,389	0.63	0.34	[redacted]	0.56	[redacted]	£42,683
Paclitaxel	11,788	0.63	0.34	[redacted]	0.56	[redacted]	£39,452
Methotrexate	11,443	0.63	0.34	[redacted]	0.56	[redacted]	£40,250
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,388	0.63	0.34	[redacted]	0.56	[redacted]	£42,659
Paclitaxel	11,787	0.63	0.34	[redacted]	0.56	[redacted]	£39,429
Methotrexate	11,442	0.63	0.34	[redacted]	0.56	[redacted]	£40,227
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,436	0.65	0.35	[redacted]	0.54	[redacted]	£43,628
Paclitaxel	11,836	0.65	0.35	[redacted]	0.54	[redacted]	£40,317
Methotrexate	11,490	0.65	0.35	[redacted]	0.54	[redacted]	£41,134

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 20: Piecewise model scenario 2 results (without PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,381	0.63	0.34	[redacted]	0.57	[redacted]	[redacted]
Paclitaxel	11,780	0.63	0.34	[redacted]	0.57	[redacted]	[redacted]
Methotrexate	11,435	0.63	0.34	[redacted]	0.57	[redacted]	[redacted]
Cut-off point: 28 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,389	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Paclitaxel	11,788	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Methotrexate	11,443	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,388	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Paclitaxel	11,787	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Methotrexate	11,442	0.63	0.34	[redacted]	0.56	[redacted]	[redacted]
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,436	0.65	0.35	[redacted]	0.54	[redacted]	[redacted]
Paclitaxel	11,836	0.65	0.35	[redacted]	0.54	[redacted]	[redacted]
Methotrexate	11,490	0.65	0.35	[redacted]	0.54	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 21: Piecewise model scenario 2 results (with PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,381	0.63	0.34	[redacted]	0.57	[redacted]	£44,823
Paclitaxel	11,780	0.63	0.34	[redacted]	0.57	[redacted]	£41,606
Methotrexate	11,435	0.63	0.34	[redacted]	0.57	[redacted]	£42,400
Cut-off point: 28 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,389	0.63	0.34	[redacted]	0.56	[redacted]	£45,014
Paclitaxel	11,788	0.63	0.34	[redacted]	0.56	[redacted]	£41,782
Methotrexate	11,443	0.63	0.34	[redacted]	0.56	[redacted]	£42,580
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,388	0.63	0.34	[redacted]	0.56	[redacted]	£44,988
Paclitaxel	11,787	0.63	0.34	[redacted]	0.56	[redacted]	£41,759
Methotrexate	11,442	0.63	0.34	[redacted]	0.56	[redacted]	£42,556
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,436	0.65	0.35	[redacted]	0.54	[redacted]	£46,017
Paclitaxel	11,836	0.65	0.35	[redacted]	0.54	[redacted]	£42,705
Methotrexate	11,490	0.65	0.35	[redacted]	0.54	[redacted]	£43,523

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Health-state utility values based on mixed-model

In response to concerns raised by the Committee and ERG as to the analysis of utility data derived from EQ-5D-3L responses obtained in CheckMate 141, a regression analysis using a mixed model has been conducted. The mixed model approach has the benefits of accounting for autocorrelation and also reducing the discarding of data due to 'missingness' (assuming that data are missing at random). The mixed model equation was fitted to the CheckMate 141 EQ-5D data with fixed covariates included for progression status (progression free or progressed disease) and treatment arm, as well as an interaction term for treatment arm and progression status, and a random effect for subject. The output from this regression analysis is presented in Table 22, where the intercept provides the utility associated with nivolumab treatment in the progression-free state.

The health-state utility values derived from this mixed model approach are presented in Table 23. The estimates from the mixed model predict that utility in the progression-free state is similar between treatment arms. This is in contrast to the values used in the original Company Evidence Submission in which progression-free utility was higher in the nivolumab arm compared to the IC arm and is also in contrast to the evidence from the other patient-reported outcome (PRO) measures collected as part of CheckMate 141, which showed significant differences in PROs in favour of nivolumab.[16] Utility values decreased in both treatment arms from progression-free to

progressed disease status, as may be expected, with the progressed disease utility value estimated to be lower in the IC arm compared to the nivolumab arm.

Table 22: Mixed model parameter estimates

Parameter	Mean	Standard error	p-value
Intercept[a]	[redacted]	[redacted]	[redacted]
Treatment arm (IC)	[redacted]	[redacted]	[redacted]
Progression status (Progressed disease)	[redacted]	[redacted]	[redacted]
Treatment arm*progression status (IC* progressed disease)	[redacted]	[redacted]	[redacted]

[a] Intercept includes nivolumab (treatment arm) and progression free (progression status).

Abbreviations: IC: investigator's choice.
Source: CheckMate 141 utility analysis using mixed model regression. Data on File.[17]

Table 23: Health-state utilities used in the revised base case analysis

Health state	Mean utility value	
	Nivolumab	IC
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

Abbreviations: IC: investigator's choice.

With regards to the source of missing data, BMS would like to reiterate the observation made by clinical experts at the first Committee meeting that completion rates of the EQ-5D-3L questionnaire were much lower in the IC arm compared to the nivolumab arm and that this was most likely due to patients being too sick to complete the questionnaire. Assuming that patients who fail to complete an assessment are unlikely to have better health-related quality of life (HRQoL) than those that do, the reported difference in utility between the treatment arms of CheckMate 141 is likely to be biased in favour of higher utility in the IC arm.

Clinical stopping rule

The optimal duration of therapy with nivolumab is currently uncertain. Clinical stopping rules were explored in the original Company Evidence Submission to reflect the possibility that, due to the unique mechanism of action of immune-checkpoint inhibitors in restoring anti-tumour immunity, it may be feasible to stop treatment with nivolumab for patients who have not yet progressed and still maintain clinical benefit. Evidence to support the stopping of treatment for patients who are responding to nivolumab is available from the CheckMate 003 trial in which treatment was continued up to 96 weeks.[8] Ongoing responses after treatment cessation were observed in this trial for patients with advanced NSCLC who had completed 96 weeks of therapy with nivolumab (see Section 5.24 of the original Company Evidence Submission). This has been accepted for nivolumab in previous appraisals [TA384 and TA400],[18, 19] and a treatment stopping rule has also been incorporated in the guidance for pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428], which states that, "*pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression*."[11]

Expert clinical opinion on treatment duration with nivolumab in SCCHN is clear in that patients would not be expected to receive nivolumab indefinitely.[10] Specifically, based on feedback from a panel of eight international clinicians (including one UK clinician), treatment duration was not expected to exceed three years, with treatment likely to be stopped much sooner.[10]

To account for the possibility that patients in clinical practice may stop treatment with nivolumab prior to disease progression, the revised base case analysis includes a 2-year clinical stopping rule in which only a proportion of patients who are still receiving treatment with nivolumab are modelled to remain on treatment with nivolumab at this time point, with all other parameters remaining the same. Using the revised base case generalised-gamma distribution to extrapolate TTD, it is predicted that approximately 3% of patients would still be receiving nivolumab after two years; the stopping rule at two years therefore affects only a small proportion of patients. [redacted].[14, 15]

Cost-effectiveness results are presented in in Table 4 (without PAS for nivolumab) and Table 5 (with PAS for nivolumab) assuming that 25%, 50% or 75% of patients still receiving nivolumab at two years remain on treatment at this time point. The revised base case used the 25% value, which is consistent with the proportion used in TA428.[11] With only approximately 3% of nivolumab patients still receiving treatment at two years, applying these proportions results in only 2.25%, 1.5%, and <1% of all the patients who were initiated on nivolumab therapy, respectively, stopping treatment at this time point as a result of the stopping rule. Cost-effectiveness results are also presented in Table 6 (without PAS for nivolumab) and Table 7 (with PAS for nivolumab) for a scenario in which no clinical stopping rule is applied.

Response 3.1

- alternative scenario analyses applied to the revised base case, that explore:
  - waning of the incremental treatment effect of nivolumab over time

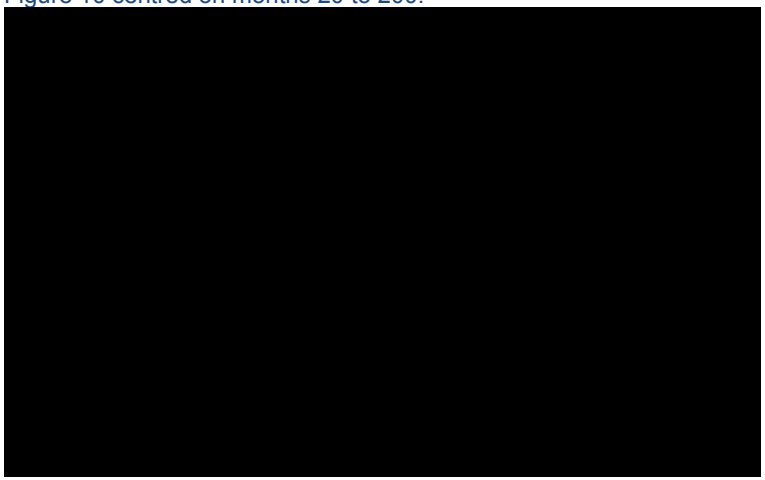
Scenario analyses have been conducted in which the treatment effect of nivolumab has been reduced from a given time point in the model. This waning of efficacy was implemented in the model by increasing the time-dependent hazard rate of death with nivolumab to a hazard rate that was the same as IC (i.e., the relative hazard rate was set to one for nivolumab versus IC), for all remaining cycles after the specified time point. This analysis therefore assumes that after the given time point there is no longer any incremental treatment benefit of nivolumab in reducing the time-dependent hazard of death relative to IC, which BMS consider to represent a strongly pessimistic assumption with regards to nivolumab efficacy, given the evidence for the potential for long-term treatment benefit with nivolumab and other immune-checkpoint inhibitors in other indications.[4-6, 20]

Separate analyses were conducted in which the time point for starting to apply this waning of efficacy was set to either five years or ten years (see Figure 10 and Figure 11 – with figures presented below centred on the respective time point). These time points were chosen based on evidence from other nivolumab indications (NSCLC; up to five years) and other immune-checkpoint inhibitors (ipilimumab for advanced melanoma; up to ten years) that demonstrate the sustained, long-term survival benefits that could be achieved by some patients treated with immune-checkpoint inhibitors.[4-6, 20]

The cost-effectiveness results for this scenario, in which the time-dependent hazard rate for death with nivolumab was increased to the same as IC after either five or ten years, are presented in Table 24 (without PAS for nivolumab) and Table 25 (with PAS for nivolumab). All other model settings for this scenario analysis were as per the revised base case analysis, including the application of a clinical stopping rule that assumed that 25% of patients who are still receiving nivolumab at two years remain on treatment. Table 26 (without PAS for nivolumab) and Table 27 (with PAS for nivolumab) present the results of the same scenario analysis with no clinical stopping rule applied.

Figure 10: Extrapolated OS with the hazard rate of death with nivolumab set to the same as IC at Year 5

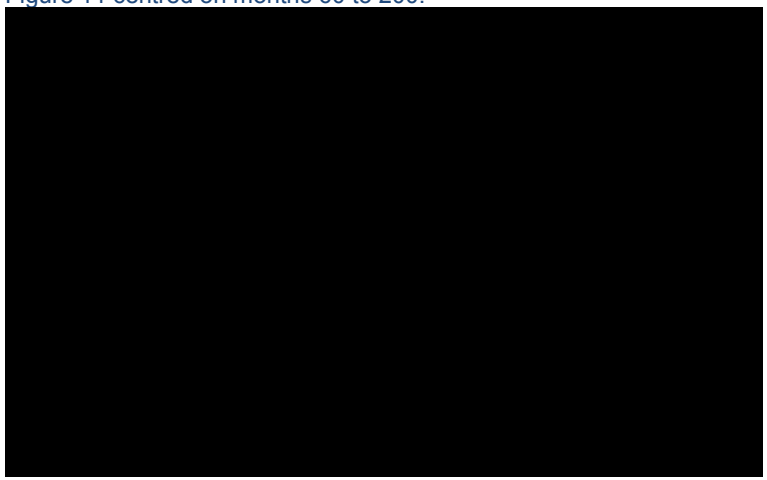
Figure 10 centred on months 20 to 200:



Abbreviations: IC: investigator's choice; OS: overall survival.

Figure 11: Extrapolated OS with the hazard rate of death with nivolumab set to the same as IC at Year 10

Figure 11 centred on months 60 to 200:



Abbreviations: IC: investigator's choice; OS: overall survival.

Table 24: Scenario results: waning of nivolumab efficacy (without PAS for nivolumab) – 25% of patients who are still receiving nivolumab at 2 years remain on treatment

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Efficacy waning after 5 years							
Nivolumab	[redacted]	1.13	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.45	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.36	[redacted]	0.45	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.36	[redacted]	0.45	[redacted]	[redacted]
Efficacy waning after 10 years							
Nivolumab	[redacted]	1.18	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.51	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.36	[redacted]	0.51	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.36	[redacted]	0.51	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 25: Scenario results: waning of nivolumab efficacy (with PAS for nivolumab) – 25% of patients who are still receiving nivolumab at 2 years remain on treatment

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Efficacy waning after 5 years							
Nivolumab	[redacted]	1.13	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.45	[redacted]	£49,465
Paclitaxel	11,881	0.67	0.36	[redacted]	0.45	[redacted]	£45,674
Methotrexate	11,536	0.67	0.36	[redacted]	0.45	[redacted]	£46,610
Efficacy waning after 10 years							
Nivolumab	[redacted]	1.18	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.51	[redacted]	£45,663
Paclitaxel	11,881	0.67	0.36	[redacted]	0.51	[redacted]	£42,184
Methotrexate	11,536	0.67	0.36	[redacted]	0.51	[redacted]	£43,043

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 26: Scenario results: waning of nivolumab efficacy (without PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Efficacy waning after 5 years							
Nivolumab	[redacted]	1.13	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.45	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.36	[redacted]	0.45	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.36	[redacted]	0.45	[redacted]	[redacted]
Efficacy waning after 10 years							
Nivolumab	[redacted]	1.18	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.51	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.36	[redacted]	0.51	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.36	[redacted]	0.51	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 27: Scenario results: waning of nivolumab efficacy (with PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Efficacy waning after 5 years							
Nivolumab	[redacted]	1.13	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.45	[redacted]	£52,200
Paclitaxel	11,881	0.67	0.36	[redacted]	0.45	[redacted]	£48,408
Methotrexate	11,536	0.67	0.36	[redacted]	0.45	[redacted]	£49,344
Efficacy waning after 10 years							
Nivolumab	[redacted]	1.18	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.51	[redacted]	£48,173
Paclitaxel	11,881	0.67	0.36	[redacted]	0.51	[redacted]	£44,693
Methotrexate	11,536	0.67	0.36	[redacted]	0.51	[redacted]	£45,552

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Response 3.2

- alternative scenario analyses applied to the revised base case, that explore:
  - a range of plausible cut points during the trial period after which the parametric model is fitted to extrapolate the trial data

A number of analyses using different cut-off points as part of the piecewise approach to modelling OS have been explored, as described in Response 2. As described in this part of our response, these piecewise analyses were not considered appropriate for the extrapolation of long-term survival with nivolumab, based on clinical evidence available from other nivolumab indications with trials of longer follow-up.

Response 3.3

- alternative scenario analyses applied to the revised base case, that explore:
  - diminishing quality-of-life benefits and duration of these benefits

In order to account for deterioration in HRQoL over time, a scenario analysis has been conducted in which HRQoL is not only modelled to decline from the progression-free to the progressed disease health state (as per the original and revised base case), but is also modelled to decline in the 30 days prior to death. The use of time-to-death to adjust utility values has previously been used in appraisals submitted to NICE for another PD-L1 inhibitor (pembrolizumab for PD-L1 positive NSCLC after chemotherapy [TA428]).[11]

For this scenario analysis, the adjustment to utility was implemented in the model as a disutility, which was applied similarly to the one-off cost for end-of-life care that was included in the original Company Evidence Submission (i.e., applied in each cycle based on the proportion of patients that died in that cycle). The disutility value used in this analysis (-0.355) was based on the difference in utility between patients in the progressed disease state with time-to-death of ≥30 days and <30 days, as used in the model submitted to NICE in TA428.[11]

The cost-effectiveness results for this scenario, in which the decline in HRQoL associated with the 30 days prior to death is applied, are presented in Table 28 (without PAS for nivolumab) and Table 29 (with PAS for nivolumab). All other model settings for this scenario analysis were as per the revised base case analysis, including the application of a clinical stopping rule that assumed that 25% of patients who are still receiving nivolumab at two years remain on treatment. Table 30 (without PAS for nivolumab) and Table 31 (with PAS for nivolumab) present the results of the same scenario analysis with no clinical stopping rule applied.

Table 28: Scenario results: diminishing utility based on time-to-death (without PAS for nivolumab) – 25% of patients who are still receiving nivolumab at 2 years remain on treatment

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.34	[redacted]	0.52	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.34	[redacted]	0.52	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.34	[redacted]	0.52	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 29: Scenario results: diminishing utility based on time-to-death (with PAS for nivolumab) – 25% of patients who are still receiving nivolumab at 2 years remain on treatment

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.34	[redacted]	0.52	[redacted]	£44,580
Paclitaxel	11,881	0.67	0.34	[redacted]	0.52	[redacted]	£41,188
Methotrexate	11,536	0.67	0.34	[redacted]	0.52	[redacted]	£42,026

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 30: Scenario results: diminishing utility based on time-to-death (without PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.34	[redacted]	0.52	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.34	[redacted]	0.52	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.34	[redacted]	0.52	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs: life-years; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Table 31: Scenario results: diminishing utility based on time-to-death (with PAS for nivolumab) – no clinical stopping rule

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.34	[redacted]	0.52	[redacted]	£47,027
Paclitaxel	11,881	0.67	0.34	[redacted]	0.52	[redacted]	£43,635
Methotrexate	11,536	0.67	0.34	[redacted]	0.52	[redacted]	£44,472

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

Response 4

- subgroup analyses according to the expression of programmed death receptor ligand 1 (PD-L1; 1 or more, or less than 1) based on the revised base case.

Subgroup analyses of the cost-effectiveness of nivolumab, according to PD-L1 expression (≥1% or <1%), were not presented in original Company Evidence Submission. The reasons for not presenting these analyses at the time were as follows:

- CheckMate 141 was not powered to show a difference between the PD-L1 subgroups; so any conclusions are inherently uncertain
- PD-L1 testing is in its infancy. Whilst PD-L1 testing is a useful starting point, this single marker, analysed at a single point in time, from a limited sample size is unlikely to be useful as a sole marker or determinant of response/toxicity. Given the complexity of the immune system, the number of potential biomarkers and more importantly, that the immune response is a highly dynamic process, it is likely that a panel of markers, yet to be defined, are likely needed.

Furthermore, it is not expected that the European Medicines Agency will specify whether patients are required to have certain expression levels of PD-L1 as part of the licensed indication for nivolumab as a treatment for R/M SCCHN.

Given the above, BMS believe that it would not be appropriate for decision making in this appraisal to focus on PD-L1 subgroups. As a result, BMS declines the opportunity to present subgroup analyses based on PD-L1 expression here and notes that subgrouping by PD-L1 was not specified in the final scope of this appraisal based on consultee feedback at the scoping stage.[21]

[redacted], [14, 15] and have been accepted by NICE in their appraisals of nivolumab as a treatment for advanced melanoma (either as monotherapy [TA384] or in combination with ipilimumab [TA400]).[18, 19]

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Appendix 1: Overview of clinical-effectiveness results from the initial database lock of CheckMate 141

Table 32: Overview of clinical effectiveness results from CheckMate 141 – all-randomised population

Outcome[a]	Nivolumab (n=240)	IC (n=121)
Overall Survival		
Deaths, n (%)	133 (55.4)	85 (70.2)
Median OS, months (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
HR for death with nivolumab (97.73% CI; p-value)[b]	0.70 (0.51, 0.96; p=0.0101)	
1-year survival rate, % (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)
Progression-free survival[c]		
Events, n (%)	190 (79.2)	103 (85.1)
Median PFS, months (95% CI)	2.0 (1.9, 2.1)	2.3 (1.9, 3.1)
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)	
6-month PFS rate, % (95% CI)	19.7 (14.6, 25.4)	9.9 (5.0, 16.9)
Tumour response[c]		
ORR, n (%) [95% CI]	32 (13.3) [9.3, 18.3]	7 (5.8) [2.4, 11.6]
Median TTR, months (range)	2.1 (1.8–7.4)	2.0 (1.9–4.6)

[a] Results are presented from the initial database lock of 18th December 2015 for OS and from the database lock of 5th May 2016 for PFS and tumour response.
[b] The pre-specified boundary for statistical significance required the p-value to be less than 0.0227; 95% CI were 0.53, 0.92
[c] Disease progression and tumour response were assessed by the investigator using RECIST version 1.1

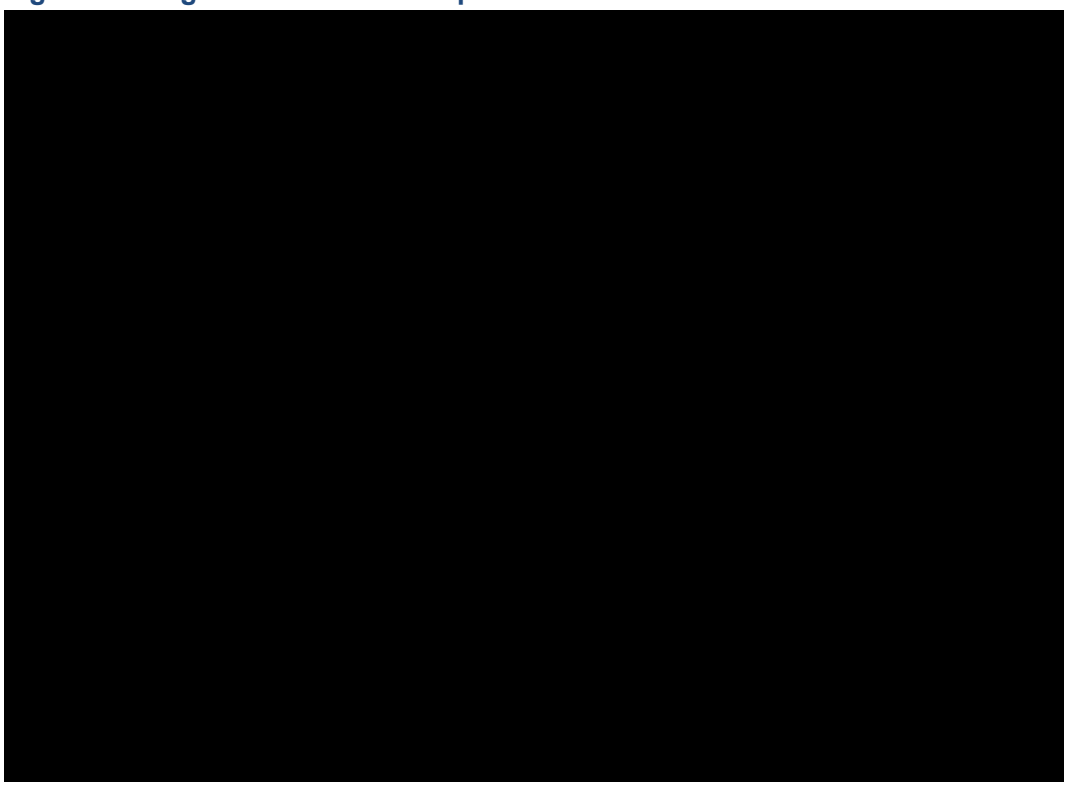
Abbreviations: CI: confidence intervals; HR: hazard ratio; IVRS: interactive voice response system; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumours; TTR: time to response.
Source: Gillison et al. (2016),[2] Ferris et al. (2016)[22] and CheckMate 141 CSR (7th June 2016)[23]

Appendix 2: Selection of parametric curves for the revised base case analysis

Extrapolation models for OS

Figure 12 shows the log cumulative hazard plot for OS based on the latest available data cut for OS from CheckMate 141 (20th September 2016). Due to the fact that the curves are not parallel and can be seen to overlap each other at several time points before separating from approximately 4 months on, it is evident that an assumption of proportional hazards does not hold. Given this, and the availability of patient-level data for both the nivolumab arm and IC arm of CheckMate 141, the fitting of independent parametric survival distributions for OS to nivolumab and the comparators was pursued in line with points 1 and 2 in the guidance summary above.

Figure 12: Log cumulative hazard plot of OS for nivolumab versus IC



Abbreviations: IC: investigator's choice; OS: overall survival.

The full range of parametric survival distributions specified in the DSU were explored as independent models for OS of nivolumab and comparator efficacy. In addition to this, spline-based models were also explored.

Table 33 and Table 34 summarise the AIC/BIC values for the variety of independent parametric distributions explored for OS for nivolumab and for IC of therapy. In terms of statistical fit, the 2-spline odds and loglogistic were the best-fitting curves for nivolumab and IC, respectively, but neither was the best-fitting for the alternative therapy. Taking into account statistical fit across both treatment arms, the lognormal distribution provides the best statistical fit to the data, being the second-best fitting distribution in each arm with differences in AIC values versus the best-fitting curves that are so small as to be meaningless as a differentiator.

Table 33: Summary of goodness-of-fit data for nivolumab OS models

Distribution	AIC	BIC
Exponential	1255.72	1259.20
Weibull	1257.55	1264.51
Gamma	1257.72	1264.68
Gompertz	1255.41	1262.37
Lognormal	1249.75	1256.71
Loglogistic	1252.19	1259.15
Generalised-gamma	1251.08	1261.52
Spline models:		
1-spline hazard	1252.07	1262.51
1-spline odds	1254.05	1264.49
1-spline normal	1251.12	1261.57
2-spline hazard	1250.94	1264.87
2-spline odds	1249.55	1263.47
2-spline normal	1250.64	1264.56

Table 34: Summary of goodness-of-fit data for IC of therapy OS models

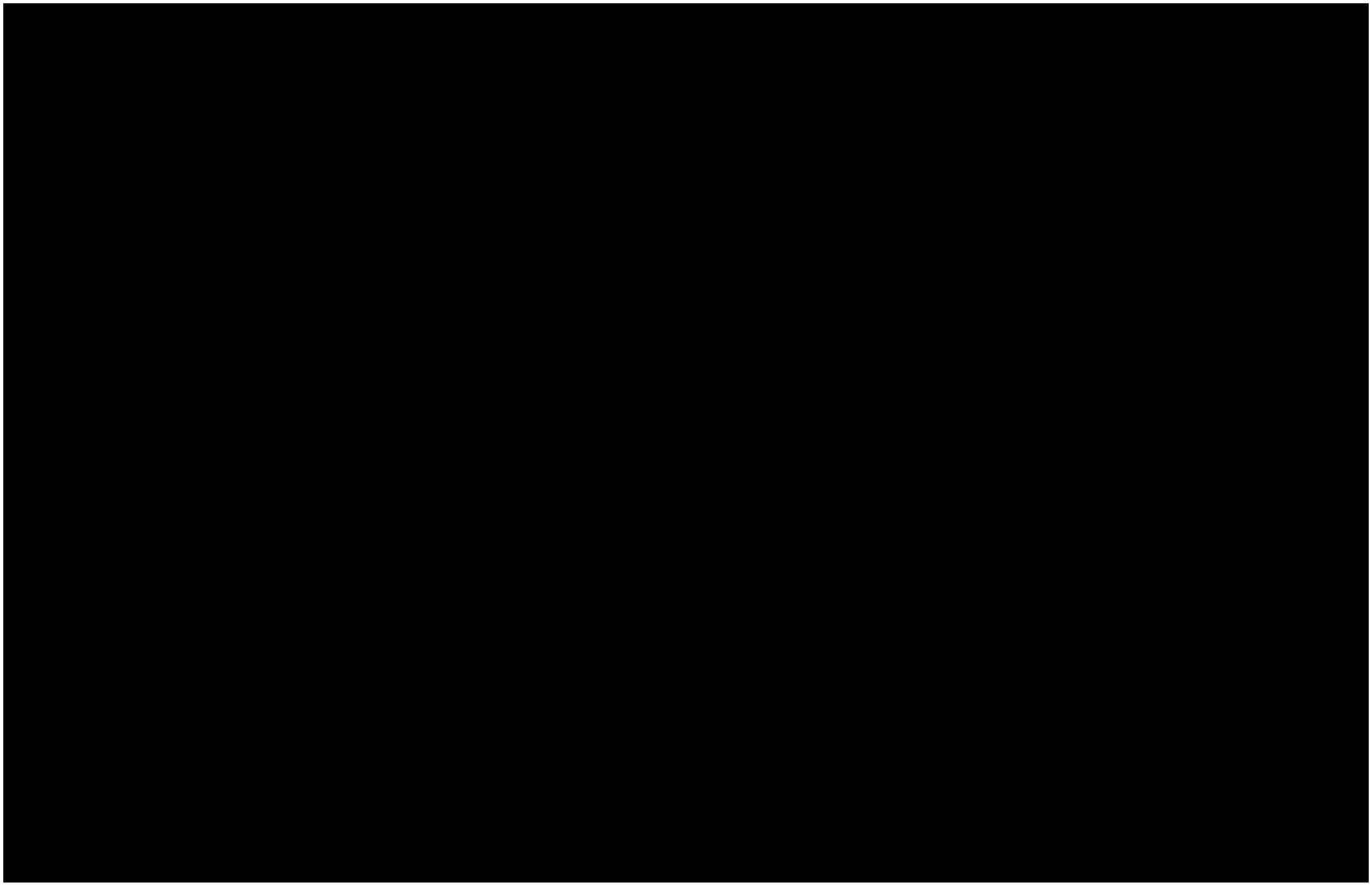
Distribution	AIC	BIC
Exponential	638.74	641.53
Weibull	636.24	641.84
Gamma	633.43	639.02
Gompertz	640.69	646.28
Lognormal	626.33	631.92
Loglogistic	626.21	631.80
Generalised-gamma	628.27	636.65
Spline models:		
1-spline hazard	629.05	637.44
1-spline odds	628.19	636.57
1-spline normal	628.11	636.50
2-spline hazard	630.49	641.67
2-spline odds	630.19	641.37
2-spline normal	629.52	640.71

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; OS: overall survival.

The long-term OS extrapolations for nivolumab and IC with each of the above models are presented in Figure 13 (for nivolumab) and Figure 14 (for IC).

Figure 13: Long-term OS extrapolation of all models - nivolumab



Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Figure 14: Long-term OS extrapolation of all models – investigator's choice

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Mean OS predicted by each of these models are provided in Table 35. Whereas mean OS values were fairly consistent across models for the IC arm (range 6.0 to 9.5), the predicted mean OS values were sensitive to the choice of survival model for OS in the nivolumab arm (range 11.6 to 17.4), thus reflecting the more mature data available from the CheckMate 141 trial for the IC arm ([redacted]% of patients had died), compared to the nivolumab arm ([redacted]% of patients had died).[1]

Table 35: Summary of predicted mean OS values for nivolumab and investigator's choice

Survival model	Predicted mean OS (months)	
	Nivolumab	Investigator's choice
Exponential	11.6	8.1
Weibull	11.7	7.9
Gamma	11.6	7.9
Gompertz	14.9	8.0
Lognormal	15.8	8.7
Loglogistic	17.4	9.4
Generalised-gamma	14.3	8.5
Spline models:		
1-spline hazard	12.8	8.3
1-spline odds	17.9	9.5
1-spline normal	14.8	8.5
2-spline hazard	12.0	8.5
2-spline odds	14.6	9.5
2-spline normal	13.3	6.0

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: OS: overall survival.

Selection of the base case OS survival model

The lognormal was the best-fitting curve when both the nivolumab and IC arms of CheckMate 141 were considered, based on AIC/BIC values (see Table 33 and Table 34). Visual inspection also indicated a satisfactory fit to the trial data (see Figure 15). Moreover, the lognormal produced estimates of OS that did not generate logical inconsistency with the long-term estimates of PFS and TTD. Additionally, the resultant probability of mortality within the next year, when using the lognormal curve, remained higher than for the general population at all time points within the 20-year time horizon, as may be expected for patients with R/M SCCHN, and without explicitly modelling the possibility of an immuno-oncology effect observed in other indications.[4-6] The lognormal was therefore proposed as the survival model for the base case analysis.

Figure 15: Plot of lognormal curve fit to Kaplan-Meier data for nivolumab and IC (OS)

Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; OS: overall survival.

Extrapolation models for PFS

Figure 16 shows the log cumulative hazard plot for PFS based on the latest available data cut for PFS from CheckMate 141 (20th September 2016). Due to the fact that the curves are not parallel and can be seen to overlap each other at several time points before separating from approximately 5 months onwards, it is evident that an assumption of proportional hazards does not hold. Given this, and the availability of patient-level data, the fitting of independent parametric survival distributions for PFS to nivolumab and the comparators was pursued.

Figure 16: Log cumulative hazard plot of PFS for nivolumab versus IC

Abbreviations: IC: investigator's choice; KM: Kaplan Meier; PFS: progression-free survival.

As for OS, the full range of parametric survival distributions specified in the DSU were explored as independent models for PFS of nivolumab and comparator efficacy, in addition to spline-based models. Table 36 and Table 37 summarise the AIC/BIC values for the various survival models explored for PFS for nivolumab and for IC.

Table 36: Summary of goodness-of-fit data for nivolumab PFS models

Distribution	AIC	BIC
Exponential	1038.16	1041.64
Weibull	1039.45	1046.41
Gamma	1039.10	1046.06
Gompertz	1013.43	1020.39
Lognormal	973.50	980.46
Loglogistic	963.74	970.70
Generalised-gamma	963.33	973.78
Spline models:		
1-spline hazard	939.49	949.93
1-spline odds	936.37	946.81
1-spline normal	955.75	966.19
2-spline hazard	N/A	N/A
2-spline odds	927.14	941.06
2-spline normal	927.03	940.95

Table 37: Summary of goodness-of-fit data for IC of therapy PFS models

Distribution	AIC	BIC
Exponential	464.55	467.35
Weibull	450.61	456.20
Gamma	443.54	449.13
Gompertz	465.01	470.60
Lognormal	437.54	443.14
Loglogistic	435.22	440.82
Generalised-gamma	439.14	447.52
Spline models:		
1-spline hazard	439.59	447.97
1-spline odds	437.12	445.51
1-spline normal	438.64	447.02
2-spline hazard	440.68	451.86
2-spline odds	439.09	450.27
2-spline normal	439.50	450.68

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; PFS: progression-free survival.

For nivolumab, the best-fitting models by AIC/BIC were the loglogistic, lognormal and generalised-gamma distributions, as well as several of the spline models (2-spline normal, 2-spline odds, and 1 spline odds, in particular). For IC, the best-fitting model by AIC/BIC was the loglogistic, followed by the 1-spline odds and 1-spline normal, and the lognormal and generalised-gamma distributions.

The long-term PFS extrapolations for nivolumab and IC with each of the above models are presented in Figure 17 (for nivolumab) and Figure 18 (for IC).

Mean PFS predicted by each of these models are provided in Table 38. The mean PFS values for nivolumab predicted by the spline models were notably higher than the non-spline distributions. The prolonged PFS predicted by the spline models was driven by small patient numbers in the tail of the Kaplan-Meier curve and is therefore associated with a considerable degree of uncertainty. Given the implausibly high mean PFS predicted by these spline models, only non-spline models were considered further in the selection of the base case PFS model.

Mean PFS values from the IC arm, on the other hand, were relatively similar across all models explored, and, when combined with the choice of TTD curve (see next section), satisfied the original ERG concern that TTD should not be greater than PFS in the IC arm given the trial design of treatment until progression, unacceptable toxicity or withdrawal of consent. Given that both treatment beyond progression and treatment discontinuation due to unacceptable toxicity or withdrawal of consent was permitted in the nivolumab arm, no such restriction exists for the nivolumab arm with regards to the relationship between PFS and TTD. However, the within trial mean from the latest database lock of CheckMate 141 showed that within trial mean PFS is [redacted] months whilst within trial mean TTD is [redacted] months ([redacted] months in both arms), which supports the results arising from the choice of PFS and TTD curves for nivolumab in the base case analysis (i.e., [redacted]).

Table 38: Summary of predicted mean PFS values for nivolumab and investigator's choice

Survival model	Predicted mean PFS (months)	
	Nivolumab	Investigator's choice
Exponential	5.1	3.9
Weibull	5.2	3.8
Gamma	5.1	3.7
Gompertz	12.5	3.8
Lognormal	5.1	3.8
Loglogistic	4.9	4.0
Generalised-gamma	6.0	3.8
Spline models:		
1-spline hazard	9.4	3.8
1-spline odds	9.3	3.9
1-spline normal	6.8	3.8
2-spline hazard	N/A	3.8
2-spline odds	11.1	3.9
2-spline normal	10.4	3.8

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: PFS: progression-free survival.

Figure 17: Long-term PFS extrapolation of all models – nivolumab

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Figure 18: Long-term PFS extrapolation of all models – investigator's choice

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Selection of the base case PFS survival model

With the spline models excluded on the basis of clinical implausibility with regards to mean PFS estimates for the nivolumab arm, the best-fitting non-spline models were inspected for visual fit to the Kaplan-Meier data from CheckMate 141. As each distribution appeared to fit the IC arm similarly well (see Table 37) and produced similar mean PFS estimates (see Table 38), the choice of distribution for the base case analysis was primarily determined by fit to the nivolumab arm.

The generalised-gamma and loglogistic distributions provided a better fit for the nivolumab arm on the basis of AIC than the lognormal distribution, with a difference in AIC that could be considered meaningful. The generalised-gamma distribution was noted to be the best statistical fit to nivolumab once the spline models had been excluded (see Table 36). On visual inspection, the generalised-gamma distribution was also considered to more closely follow the Kaplan-Meier curve for nivolumab (in the months following Month 5, at least – at which point the Kaplan-Meier curves for IC and nivolumab had separated) (see Figure 19). With the preference towards fit to the nivolumab arm, the generalised-gamma distribution was therefore chosen for the base case analysis.

Figure 19: Plot of generalised-gamma curve fit to Kaplan-Meier data for nivolumab and IC (PFS)

Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; PFS: progression-free survival.

Extrapolation models for TTD

Figure 20 provides the log cumulative hazard plot for TTD based on the latest available data cut from CheckMate 141. Due to the fact that the curves cross an assumption of proportional hazards does not appear to hold. With the availability of patient-level data for TTD, independent parametric distributions were explored for TTD.

Figure 20: Log cumulative hazard plot of TTD for nivolumab versus IC

Abbreviations: IC: investigator's choice; TTD: time to discontinuation.

As for OS and PFS, the full range of parametric survival distributions specified in the DSU TSD were explored as independent models for TTD of nivolumab and IC, in addition to spline-based models.

Table 39 and Table 40 summarise the AIC/BIC values for the variety of independent parametric distributions explored for TTD for nivolumab and for IC.

Table 39: Summary of goodness-of-fit data for nivolumab TTD models

Distribution	AIC	BIC
Exponential	1101.05	1104.52
Weibull	1075.45	1082.37
Gamma	1083.51	1090.44
Gompertz	1056.33	1063.26
Lognormal	1082.41	1089.33
Loglogistic	1060.38	1067.31
Generalised-gamma	1069.95	1080.35
Spline models:		
1-spline hazard	1069.09	1079.48
1-spline odds	1055.56	1065.95
1-spline normal	1063.55	1073.94
2-spline hazard	1048.29	1062.14
2-spline odds	1045.26	1059.12
2-spline normal	1045.30	1059.15

Table 40: Summary of goodness-of-fit data for IC of therapy TTD models

Distribution	AIC	BIC
Exponential	416.69	419.40
Weibull	416.24	421.66
Gamma	417.25	422.67
Gompertz	417.25	422.67
Lognormal	454.30	459.72
Loglogistic	435.49	440.91
Generalised-gamma	417.39	425.52
Spline models:		
1-spline hazard	415.14	423.27
1-spline odds	N/A	N/A
1-spline normal	N/A	N/A
2-spline hazard	409.01	419.85
2-spline odds	411.69	422.53
2-spline normal	N/A	N/A

The distribution selected for the base is shaded grey – see later sections for justification of selection
N/A refers to distributions that could not be parameterised

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; IC: investigator's choice; TTD: time to discontinuation.

For both nivolumab and IC, the models with the best statistical fit were spline models (2-spline odds and 2-spline hazard, respectively). However, as discussed in the original Company Evidence Submission (see Section 5.3), these spline models were avoided where simpler models were seen to provide sufficient fit to the data. Consequently, only non-spline models were presented in the base case for OS, PFS and TTD in the original Company Evidence Submission

and the use of non-spline models was accepted by the ERG in their assessment of the original Company Evidence Submission.

Of the non-spline models, the Gompertz, loglogistic and generalised-gamma were associated with the best statistical fit for nivolumab and the Weibull, exponential and Gompertz were the best-fitting for IC. The long-term TTD extrapolations for nivolumab and IC with each of the above models are presented in Figure 21 (for nivolumab) and Figure 22 (for IC).

Mean TTD values predicted by each of these models are provided in Table 41. For IC, mean TTD did not vary considerably between models (spline and non-spline). In contrast, the mean TTD for nivolumab ranged between five and seven months for the majority of curves, with higher mean TTD predicted by the Gompertz and 2-spline odds models.

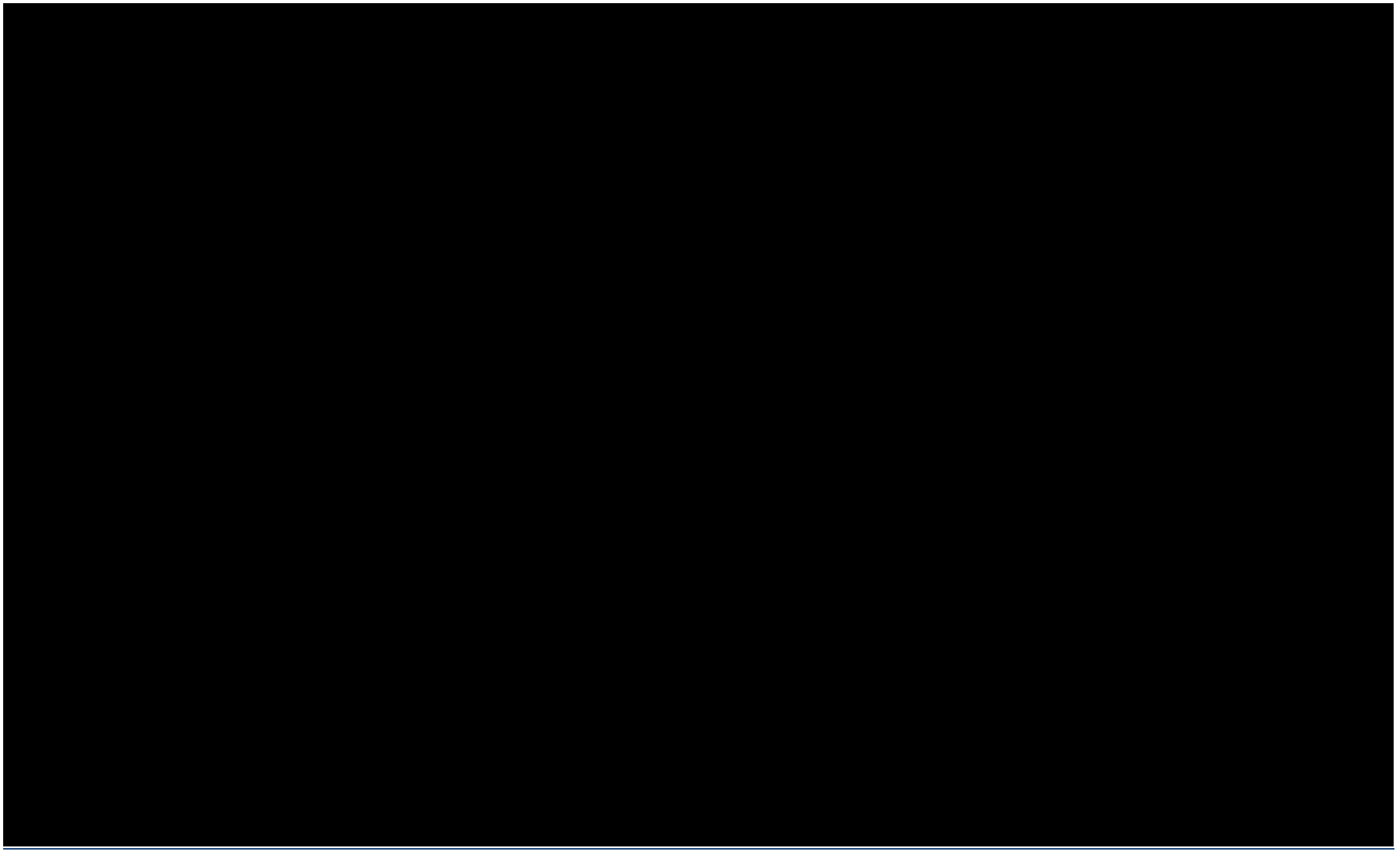
Table 41: Summary of predicted mean TTD values for nivolumab and investigator's choice

Survival model	Predicted mean TTD (months)	
	Nivolumab	Investigator's choice
Exponential	4.9	2.9
Weibull	5.1	2.9
Gamma	5.1	2.9
Gompertz	15.1	2.9
Lognormal	7.2	3.8
Loglogistic	7.5	4.1
Generalised-gamma	[redacted]	[redacted]
Spline models:		
1-spline hazard	5.4	2.9
1-spline odds	5.9	N/A
1-spline normal	5.3	N/A
2-spline hazard	6.7	2.9
2-spline odds	8.1	3.0
2-spline normal	7.1	N/A

The distribution selected for the base is shaded grey – see later sections for justification of selection

Abbreviations: TTD: time to discontinuation.

Figure 21: Long-term TTD extrapolation of all models – nivolumab



Abbreviations: KM: Kaplan-Meier; TTD: time to discontinuation.

Figure 22: Long-term TTD extrapolation of all models – investigator's choice

Abbreviations: KM: Kaplan-Meier; TTD: time to discontinuation.

Selection of the base case TTD survival model

Given the preference for selecting non-spline distributions where possible, the next best fitting (non-spline) models were considered for inclusion in the base case analysis. Of these, the Gompertz, loglogistic and generalised-gamma were associated with reasonable statistical fit to both the nivolumab and IC arms, with the Weibull and exponential distributions removed from consideration due to their poor statistical fit with nivolumab.

The loglogistic produced a close visual fit to the nivolumab Kaplan-Meier curve but was seen to poorly fit the IC curve. An improved visual fit to the IC curve was seen with the generalised-gamma but this tended to overestimate the number of patients on treatment in the early phase of the nivolumab Kaplan-Meier curve. The visual fit for the Gompertz distribution was considered to be reasonable for both IC and nivolumab.

With regards to the relationship between TTD and OS (using the preferred lognormal distribution for OS), the extrapolated OS fell below the extrapolated TTD for both nivolumab and IC when using the loglogistic distribution for TTD and for nivolumab when using the Gompertz distribution for TTD. In contrast, the generalised-gamma distribution resulted in no such logical inconsistencies for either IC or nivolumab. In order to avoid th6

ese inconsistencies, the generalised-gamma distribution was therefore chosen for the base case analysis (see Figure 23).

Figure 23: Plot of generalised-gamma fit to Kaplan-Meier data for nivolumab and IC (TTD)

Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; TTD: time to discontinuation.

Appendix 3: Changes to the cost-effectiveness model

Table 42: List of changes to the cost-effectiveness model

Change	Sheet	Cell range
Model input changes		
Parameters for the parametric curves being fitted to the model	OS	Rows 34-46 and 416-428
	PFS	Rows 34-46 and 416-428
	TTD	Rows 48-60 and 468-480
Use of clinical practice docetaxel dosing (selected as base case)	Treatment Costs	Cell L14
Utility data from the mixed model analysis (added and selected as base case)	Utility Inputs	Ranges G11:J12 and L11:O12
Kaplan-Meier data from the latest database lock of CheckMate 141 added	KM Data	Columns E, F, H, I, L, M, O, P, S, T, V, and W
Model features added		
Inclusion of piecewise analyses (exponential and lognormal distributions at various cut-off points)	OS	Ranges CV34:DM410, EA34:ER410, and CW416:EF792
	PFS	Ranges CV34:DQ410 and CW416:DR792
	TTD	Ranges CS48:DN424 and CT468:DO844
Inclusion of waning treatment effect curve	OS	Range DO34:DY410
Ability to have reduced numbers on treatment after a given time point (for stopping rule)	Treatment Costs	Range E117:I124

in collaboration with:

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INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy: critique of new evidence submitted BMS on February 3rd 2017

Produced by Kleijnen Systematic Reviews Ltd. (KSR) in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)

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Academic in confidence (AiC) data are highlighted in yellow throughout the report.

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Contributions of authors
Nigel Armstrong acted as project lead as well as systematic reviewer and health economist on this assessment, critiqued the clinical effectiveness methods and evidence as well as the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Xavier Pouwels, Remziye Zaim and Ching-Yun Wei acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Robert Wolff and Rob Riemsma acted as systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore and Maiwenn Al acted as health economists on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the

underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

5-FU	5-Fluoruracil
AE	Adverse Events
AHNS	American Health and Neck Society
AIC	Akaike information criterion
AMCP	Academy of Managed Care Pharmacy
ASCO	American Society of Clinical Oncology
ASCO-QoC	ASCO Quality Care Symposium
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	Best overall response
BAHNO	British Association of Head and Neck Oncologists
BSA	Body surface area
BUP	Buparlisib
CADTH	Canadian Agency for Drugs and Technologies in Health
CCT	Controlled clinical trial
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CMR	Cochrane Methodology Register
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DALY	Disability-adjusted life year
DMC	Data monitoring committee
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EHNS	European Society of Medical Oncologists
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group performance status
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EORTC H&N35	European Organisation for Research and Treatment of Cancer head and neck questionnaire
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
EUR	Erasmus University Rotterdam
FDA	US Food and Drug Administration
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health Related Quality of Life

HTA	Health Technology Assessment
i.v.	Intravenous
IC	Investigator's choice
ICER	Incremental cost effectiveness ratio
ICUR	Incremental cost utility ratio
IDMC	Independent data monitoring committee
IPCW	Inverse probability of censoring weights
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to Treat
IVRS	Interactive voice response system
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LOE	Languages other than English
LY	Life year
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
mg	Milligram
MI	Multiple imputation
MRI	Magnetic resonance imaging
N/A	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
NSCLC	Non-small cell lung cancer
OCIU	Oxford Cancer Intelligence Unit
ORR	Objective response rate
OS	Overall survival
PAC	Paclitaxel
PAS	Patient access scheme
PBO	Placebo
PD	Progressed disease
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PF	Progression-free
PFS	Progression-free survival
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PS	Performance status
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
Q2W	Once every two weeks
Q3W	Once every three weeks
QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of life
QW	Once weekly
R/M	Relapsed or metastatic
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SC	Subcutaneous
SCC	Squamous cell carcinoma
SCCHN	Squamous cell carcinoma of the head and neck

SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results Program
SF-36	Short form 36
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
STA	Single Technology Appraisal
UMC	University Medical Centre
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
TTD	Time to treatment discontinuation
TTF	Time to failure
TTO	Time trade off
TTP	Time to progression
TTR	Time to response
UK	United Kingdom
USA	United States of America
VEGF	Vascular endothelial growth factor

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1. Response 1: updated clinical-effectiveness data from the latest data-cut of the CheckMate 141 trial

The company presented an overview of the clinical effectiveness results from the latest database lock of the CheckMate 141 trial (20th September 2016).[1] The results from Table 1 in the new submission have been presented alongside those from Table 15 of the original submission.[2] The abbreviation 'NA' was used in Table 1 to refer to the 24-month results for both overall and progression-free survival with no explanation, the most likely explanation being, given not all patients were known to have died, that some patients were lost to follow-up. Nevertheless, very little seems to have changed in terms of the comparison between nivolumab and investigator choice (IC): in particular, [redacted].

[redacted].

It was also confirmed that a [redacted] in the IC arm ([redacted]%) received subsequent immunotherapy (including nivolumab) compared to the nivolumab arm ([redacted]%) (not including [redacted]).[1] However, there was no update on the percentage who received taxanes and experimental drugs, the balance of which was in the opposite direction. [2]

The conclusions of the ERG regarding clinical effectiveness therefore remain fundamentally unchanged.

Table 1.1: Overview of clinical effectiveness results from CheckMate 141 – all-randomised population

Outcome[a]	Original company submission		New submission	
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)
Overall Survival				
Deaths, n (%)	133 (55.4)	85 (70.2)	[redacted]	[redacted]
Median OS, months (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)	[redacted]	[redacted]
HR for death with nivolumab (97.73% CI; p-value)[b]	0.70 (0.51, 0.96; p=0.0101)		[redacted]	
1-year survival rate, % (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)	[redacted]	[redacted]
18-month survival rate, % (95% CI)	NA	NA	[redacted]	[redacted]
24-month survival rate, % (95% CI)	NA	NA	[redacted]	[redacted]
Progression-free survival[c]				
Events, n (%)	190 (79.2)	103 (85.1)	[redacted]	[redacted]
Median PFS, months (95% CI)	2.0 (1.9, 2.1)	2.3 (1.9, 3.1)	[redacted]	[redacted]
HR for progression or death with nivolumab (95% CI; p-value)	0.89 (0.70, 1.1; p=0.3236)		[redacted]	
6-month PFS rate, % (95% CI)	19.7 (14.6, 25.4)	9.9 (5.0, 16.9)		
18-month PFS rate, % (95% CI)	NA	NA	[redacted]	[redacted]
24-month PFS rate, % (95% CI)	NA	NA	[redacted]	[redacted]
Tumour reponsec				
ORR, n (%) [95% CI]	32 (13.3) [9.3, 18.3]	7 (5.8) [2.4, 11.6]	[redacted]	[redacted]
Median TTR, months (range)	2.1 (1.8–7.4)	2.0 (1.9–4.6)	[redacted]	[redacted]
Median DOR, months (range)	NA	NA	[redacted]	[redacted]

Source of original company submission: Gillison 2016[3], Ferris 2016[4] and CheckMate 141 CSR (7th June 2016)[5]

Notes: [a] Results are presented from the initial database lock of 18th December 2015 for OS and from the database lock of 5th May 2016 for PFS and tumour response; [b] The pre-specified boundary for statistical significance required the p-value to be less than 0.0227, 95% CI were 0.53, 0.92. [c] Disease progression and tumour response were assessed by the investigator using RECIST version 1.1[6]

CI = confidence intervals; CS = company submission; CSR = clinical study report; HR = hazard ratio; IVRS = interactive voice response system; NA = not applicable; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours; TTR = time to response

2. Response 2

The company submitted a revised base-case cost effectiveness analysis[1]. Although it is not clear, the ERG suspects that the adjustments are made conditional on the company's updated base-case received in response to the clarification letter.[7] The following adjustments were made to this company base-case:

- Including the latest data from CheckMate 141
- Re-analyse utility data using robust methods to estimate the treatment-dependent health-state utility values, appropriately adjusting for missing data
- Incorporating the recommended dosing regimen for docetaxel used in clinical practice in England (75 mg/m^2, once every 3 weeks)

Moreover, the company provided scenario analyses (conditional on the revised company base-case) using Kaplan–Meier data for the earlier phase of the model followed by parametric curves to extrapolate to the remainder of the model time horizon (the second phase), i.e. a piecewise approach:

1. Using the log-normal distribution for the second phase (starting at 20, 36 or 48 weeks) for both treatments.
2. Using the log-normal distribution for the entire time horizon (fully parametric approach) for nivolumab while using a piecewise approach based on the exponential distribution for the second phase (starting at 20, 28, 36 or 48 weeks) for IC.

In addition, the company also provided scenarios with clinical stopping rules in which after 2 years only 25%, 50% or 75% of patients still on treatment continue the treatment (exact stopping criteria not specified). The implementation of these scenarios amounted to reducing the costs for nivolumab after 2 years, without any adjustment to the treatment effectiveness. These scenarios were not considered by the ERG because these were not requested by the committee and because it is unclear to the ERG why these scenarios should be considered plausible.

Revised base-case

The following section will summarise and critique the adjustments in the company's revised base-case (see Table 2.2 for the results).

Including the latest data from CheckMate 141

The company re-estimated the parametric time-to-event models for OS (overall survival; log-normal distribution), progression free survival (PFS; generalised-gamma distribution) and time to treatment discontinuation (TTD; generalised-gamma distribution) based on the latest data from CheckMate 141. The company used similar methods as outlined in the original CS[2] and summarised in the ERG report,[8] resulting in almost identical choices regarding stratification and selection of parametric distributions. The only exception is the preference of the generalised-gamma distribution instead of the log-logistic distribution for TTD to prevent logical inconsistencies between the curves (as was preferred by the ERG; see ERG report section 5.2.6).[8]

The company examined the plausibility of these models and considered that:

- For IC, the OS that is predicted is broadly consistent with the expectations of clinical experts for patients receiving currently-available therapies in clinical practice (see Table 8 of the additional submission by the company).[1]

- For nivolumab the OS that is predicted is [redacted] with nivolumab as a treatment for previously-treated squamous NSCLC (considering annual survival probabilities; see Table 9 of the additional submission by the company).[1]
- The log-normal distribution produced estimates of OS that did not generate logical inconsistency with the long-term estimates of PFS and TTD.

As stated in the original ERG report: the ERG considered the statistical methods used by the company for selecting the distributions for the time-to-event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis.[9]

Re-analyse utility data using robust methods

The company used a mixed model to estimate utility scores. The mixed model equation was fitted to the CheckMate 141 EQ-5D data with fixed covariates included for progression status (progression free or progressed disease) and treatment arm, as well as an interaction term for treatment arm and progression status, and a random effect for subject. See Table 2.1 for the resulting utility scores. Although the ERG agrees with the company that the mixed model approach has the benefits of accounting for autocorrelation and also reducing the discarding of data due to 'missingness' (assuming that data are missing at random), this is conditional on that the model being specified correctly. Given the lack of details (regarding methods and model diagnostics), the ERG is unable to examine whether the model is specified correctly and hence whether the missing data (one of the main concerns raised in the ERG report) are dealt with appropriately. Also, it can be questioned whether it is plausible to extrapolate the relatively high post-progression utility for nivolumab over the entire time horizon, i.e. whether this utility increase compared with IC is also applicable after treatment discontinuation.

Table 2.1: Utility scores estimated using the mixed model

Health state	Nivolumab	IC of therapy
	Mean utility value	Mean utility value
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

Source: Table 23 in additional submission by the company.[1]

Incorporating the recommended dosing regimen for docetaxel used in clinical practice

The company incorporated the recommended dosing regimen for docetaxel used in clinical practice in England (75 mg/m^2, once every 3 weeks), this is consistent with the ERG base-case (see ERG report sections 5.2.4 and 5.2.9)[8]

New ERG base-case

The ERG took the new company base-case as a starting point to produce a new ERG base-case based on the adjustments described in the ERG report. Below is a list of these adjustments. However, very few changes from the company base-case have been implemented. This is because most have already been incorporated in the company model and some of which are not possible now because they have been superseded by the new company base-case.

Fixing errors

1. Fixing errors consisted of:
    a. Adding OS, PFS and TTD as probabilistic parameters in the PSA (without incorporating the correlation between parameters)
    This is incorporated in the new company base-case.

    b. Incorporate NHS reference costs in PSA using upper and lower quartiles
    This is incorporated in the new company base-case.

    c. Changing the standard deviation into standard error for utility scores in the PSA
    The standard deviation was incorrectly labelled/incorporated as standard error in the economic model. This is incorporated in the new company base-case.

    d. Using all available baseline utility data
    The ERG had used utility estimates based on all patients with a baseline measurement (i.e. utility data from Table 29 of the clarification response). However, the new company base-case supersedes this with the re-analysis of utility data (see above).

Fixing violations

2. Adding adverse event costs (£418.91) and disutility (-0.15) for pneumonitis
    This has now been implemented.

3. Using docetaxel dosing conform to UK clinical practice
    This is incorporated in the new company base-case.

Matters of judgment

4. Using the generalised-gamma distribution for TTD
    This is incorporated in the new company base-case.

5. Using treatment independent utility
    Given the uncertainty in the estimation of the treatment dependent utility scores, the ERG judges it to be most appropriate to use treatment independent utility scores (see Section 5.2.8 of the ERG report for more details).[8] However, the new company base-case supersedes this with the re-analysis of utility data (see above).

6. Using treatment independent proportions for subsequent treatments
    This has now been implemented.

Therefore, in summary there are only three differences between the new company base-case and the new ERG base-case:

- the addition of an adverse event cost and disutility for pneumonitis,
- the use of treatment independent proportions for subsequent treatments, and
- no clinical stopping rule.

The results are shown in Table 2.3. As can be seen, there is virtually no difference to the company base-case with no clinical stopping rule, as shown in Table 2.2.

Scenario analyses using piecewise approach for overall survival (OS)

The company did not consider it appropriate to use a piecewise approach i.e. employing the Kaplan-Meier survival data for OS up to a specified time point in the model (first phase) followed by the use of an appropriate parametric curve to extrapolate survival from this cut-off point to the end of the time horizon (second phase). However, scenarios using a piecewise approach have been explored by the

company in order to address the request made by NICE. It should however be noted that the company did not explore the exponential distribution for nivolumab for the second phase as the company did not consider the exponential distribution to be a good fit and since the exponential distribution does not allow for the possibility of a plateau in the survival curve for nivolumab. Hence the company argued that the exponential distribution does not accurately reflect the durable survival benefits that nivolumab, as an immune-checkpoint inhibitor, can potentially offer some patients. Therefore the company explored two scenarios:

1. Using the log-normal distribution for the second phase (starting at 20, 36 or 48 weeks) for both treatments.
2. Using the log-normal distribution for the entire time horizon (fully parametric approach) for nivolumab while using a piecewise approach based on the exponential distribution for the second phase (starting at 20, 28, 36 or 48 weeks) for IC.

Moreover, the company stressed that the limitations with regards to the piecewise approach has been discussed in the literature.[10, 11] Specifically, the need to select an appropriate cut-off point and the issues associated with fitting curves to the latter part of the Kaplan-Meier data, where the numbers at risk are vastly reduced, have been highlighted as key concerns.[10]

Table 2.2: Company base-case and piecewise approach scenario analyses (with PAS for nivolumab)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Base-case							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	£47,086
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	£43,690
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	£44,528
Scenario 1: Piecewise approach for OS using log-normal for second phase							
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.26	[redacted]				
Docetaxel	10,682	0.77	0.41	[redacted]	0.49	[redacted]	£47,487
Paclitaxel	12,081	0.77	0.41	[redacted]	0.49	[redacted]	£44,050
Methotrexate	11,736	0.77	0.41	[redacted]	0.49	[redacted]	£44,899
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.37	[redacted]				
Docetaxel	10,777	0.82	0.43	[redacted]	0.55	[redacted]	£43,013
Paclitaxel	12,176	0.82	0.43	[redacted]	0.55	[redacted]	£39,918
Methotrexate	11,831	0.82	0.43	[redacted]	0.55	[redacted]	£40,682
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.10	[redacted]				
Docetaxel	10,499	0.68	0.37	[redacted]	0.41	[redacted]	£55,602
Paclitaxel	11,899	0.68	0.37	[redacted]	0.41	[redacted]	£51,544
Methotrexate	11,553	0.68	0.37	[redacted]	0.41	[redacted]	£52,546

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Scenario 2: Full parametric approach for nivolumab and piecewise approach for OS using exponential for second phase for IC only							
Cut-off point: 20 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,381	0.63	0.34	[redacted]	0.57	[redacted]	£44,823
Paclitaxel	11,780	0.63	0.34	[redacted]	0.57	[redacted]	£41,606
Methotrexate	11,435	0.63	0.34	[redacted]	0.57	[redacted]	£42,400
Cut-off point: 28 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,389	0.63	0.34	[redacted]	0.56	[redacted]	£45,014
Paclitaxel	11,788	0.63	0.34	[redacted]	0.56	[redacted]	£41,782
Methotrexate	11,443	0.63	0.34	[redacted]	0.56	[redacted]	£42,580
Cut-off point: 36 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,388	0.63	0.34	[redacted]	0.56	[redacted]	£44,988
Paclitaxel	11,787	0.63	0.34	[redacted]	0.56	[redacted]	£41,759
Methotrexate	11,442	0.63	0.34	[redacted]	0.56	[redacted]	£42,556
Cut-off point: 48 weeks							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,436	0.65	0.35	[redacted]	0.54	[redacted]	£46,017
Paclitaxel	11,836	0.65	0.35	[redacted]	0.54	[redacted]	£42,705
Methotrexate	11,490	0.65	0.35	[redacted]	0.54	[redacted]	£43,523

Source: Tables 7, 17 and 21 in additional submission by the company[1]
ICER: incremental cost-effectiveness; QALYs quality adjusted life-years

Table 2.3: ERG base-case (with PAS for nivolumab)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Base-case							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,459	0.67	0.36	[redacted]	0.52	[redacted]	£47,419
Paclitaxel	11,859	0.67	0.36	[redacted]	0.52	[redacted]	£44,007
Methotrexate	11,525	0.67	0.36	[redacted]	0.52	[redacted]	£44,820

3. Response 3: alternative scenario analyses applied to the revised base-case

3.1: Waning of the incremental treatment effect of nivolumab over time

The company explored additional scenarios in which the treatment effect of nivolumab versus IC has been removed from a given time point in the model (Table 3.1). This removal of incremental treatment effect was implemented in the model by increasing the time-dependent hazard rate of death with nivolumab to a hazard rate that was the same as IC (i.e. the hazard ratio was set to one for nivolumab versus IC), for all remaining cycles after the specified time point. For this purpose the company used two time points for starting to apply this removal of incremental treatment effect:

1) Removal of incremental treatment effect after 5 years
2) Removal of incremental treatment effect after 10 years

These time points were chosen based on evidence from other nivolumab indications (NSCLC; up to five years) and other immune-checkpoint inhibitors (ipilimumab for advanced melanoma; up to ten years) that demonstrate the sustained, long-term survival benefits that could be achieved by some patients treated with immune-checkpoint inhibitors.[12-15]

Table 3.1: Scenario analyses: removal of incremental treatment effect over time (with PAS for nivolumab)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Efficacy waning after 5 years							
Nivolumab	[redacted]	1.13	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.45	[redacted]	£52,200
Paclitaxel	11,881	0.67	0.36	[redacted]	0.45	[redacted]	£48,408
Methotrexate	11,536	0.67	0.36	[redacted]	0.45	[redacted]	£49,344
Efficacy waning after 10 years							
Nivolumab	[redacted]	1.18	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.51	[redacted]	£48,173
Paclitaxel	11,881	0.67	0.36	[redacted]	0.51	[redacted]	£44,693
Methotrexate	11,536	0.67	0.36	[redacted]	0.51	[redacted]	£45,552

Source: Table 27 in additional submission by the company[1]
ICER: incremental cost-effectiveness; QALYs quality adjusted life-years

3.2: A range of plausible cut points during the trial period after which the parametric model is fitted to extrapolate the trial data

This was dealt with by the company under Response 2 (see Scenario analyses using piecewise approach for overall survival (OS) above).

3.3: Diminishing quality-of-life benefits and duration of these benefits

Additional sensitivity analyses were provided with diminishing quality-of-life benefits and duration of these benefits (Table 3.2). In this scenario a one-off disutility of -0.355 was applied to the proportion of patients that died in that cycle (applied for all treatments). The disutility value used in this analysis (-0.355) was based on the difference in utility between patients in the progressed disease state with time-to-death of ≥30 days and <30 days, as used in the model submitted to NICE in TA428.[16] However, this disutility is applied to all treatments and only for the last cycle before dying. Therefore, it is unclear to the ERG how this scenario reflects the "diminishing quality-of-life benefits and duration of these benefits" scenario (as requested by the committee). As discussed in "Response 2" it can be questioned

whether it is plausible to extrapolate the relatively high post-progression utility for nivolumab over the entire time horizon (i.e. whether this utility increase compared with IC is also applicable after treatment discontinuation). For this reason, the ERG considers that this scenario analysis as requested by the committee might have been very informative. The ERG would have preferred a different implementation of this scenario than provided by the company i.e. a scenario analysis incorporating pre and post treatment discontinuation health state utilities for nivolumab (estimated using the mixed model).

Table 3.2: Scenario analyses: with diminishing quality-of-life benefits and duration of these benefits (with PAS for nivolumab)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Nivolumab	[redacted]	1.2	[redacted]				
Docetaxel	10,482	0.67	0.34	[redacted]	0.52	[redacted]	£47,027
Paclitaxel	11,881	0.67	0.34	[redacted]	0.52	[redacted]	£43,635
Methotrexate	11,536	0.67	0.34	[redacted]	0.52	[redacted]	£44,472

Source: Table 31 in additional submission by the company[1]
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; PAS: Patient Access Scheme; QALYs: quality-adjusted life years.

4. **Response 4: subgroup analyses according to the expression of programmed death receptor ligand 1 (PD-L1; 1 or more, or less than 1) based on the revised base-case.**

These analyses were not performed by the company. The reasons for not presenting these analyses can be summarised as:

1) CheckMate 141 was not powered to show a difference between the PD-L1 subgroups; so any conclusions are inherently uncertain
2) PD-L1 testing is unlikely to be useful as a sole marker or determinant of response/toxicity. Instead, a panel of markers, yet to be defined, are likely needed.
3) It is not expected that the European Medicines Agency will specify whether patients are required to have certain expression levels of PD-L1 as part of the licensed indication for nivolumab as a treatment for R/M SCCHN.
4) Subgrouping by PD-L1 was not specified in the final scope of this appraisal based on consultee feedback at the scoping stage.[17]
5) [redacted][18, 19 20, 21] and have been accepted by NICE in their appraisals of nivolumab as a treatment for advanced melanoma (either as monotherapy [TA384] or in combination with ipilimumab [TA400]).[22-25]

The ERG therefore cannot comment on these analyses. It is the view of the ERG that, whilst the points that the company cites as reasons for not doing the analyses are valid, they do not appear to be sufficient ground for refusing to perform them. In particular, lack of power to detect a difference should be cited more as a limitation to any analysis rather than a reason not to perform it and the fact that other markers might also be prognostic does not preclude the prognostic value of PD-L1 as a single marker. The importance of PD-L1 not being part of the licenced indication and its subgrouping not being in the scope is a matter for NICE and the committee to determine.

With regards to previous technology appraisal guidance, the role of precedence is a matter for the committee. It is worth noting in TA384 the committee noted that: "comparatively better outcomes were seen in people with positive PD-L1 expression." (p.28)[24] In TA400 the committee: "…concluded that PD-L1 expression may be one of the factors that influence clinical decision making, but it would not be appropriate for NICE to base recommendations on PD-L1 expression at present." (p.11)[25] Despite the committee identifying difference by PD-L1 status, it is unclear to the ERG precisely why cost-effectiveness analysis by sub-group was not required and why NICE considered it inappropriate thereby to make recommendations by subgroup.

5. References

[1] Bristol-Myers Squibb Pharmaceuticals Ltd. *Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]. Single technology appraisal (STA): final company response to request for additional evidence*. Uxbridge, UK: Bristol-Myers Squibb Pharmaceuticals Ltd., 3rd February 2017 [accessed 6.2.17]. 56p.

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To clarify the effect of different assumptions to predict (long-term) overall survival (OS), the ERG presented detailed information regarding the predicted OS in Tables 1-3 and Figures 1-3. Moreover, the ERG provided additional scenario analyses as requested by the appraisal committee (conditional upon the updated ERG base-case):

1. Using a piecewise approach to predict OS; based Kaplan-Meier curves (first phase) and Exponential distribution (second phase) with the following cut-offs:
    a. 20 weeks
    b. 28 weeks
    c. 36 weeks
    d. 48 weeks
2. Using treatment independent utility values (see overview of utilities in Table 4)

In addition to the requested analyses, the ERG has explored a scenario, to reflect its reservations regarding the relatively high post progression utility for nivolumab (e.g. whether this utility increase compared with IC is also applicable after treatment discontinuation). In this scenario the ERG applied a disutility of 0.149 (difference in post progression utility between nivolumab and IC) for patients that discontinued nivolumab treatment. The results of the analyses are provided in Table 5.

Table 1: Full parametric approach to predict OS; based on Log-normal distribution

	Nivolumab	IC	Difference	Nivolumab	IC	Difference
	Log-normal			Log-normal (original CS)		
Months	**OS**					
12	32.9%	19.2%	13.7%	35.2%	18.1%	17.0%
24	16.5%	5.7%	10.9%	18.8%	5.1%	13.7%
36	10.0%	2.3%	7.7%	11.8%	2.0%	9.9%
48	6.7%	1.1%	5.6%	8.2%	0.9%	7.3%
60	4.7%	0.6%	4.1%	6.0%	0.5%	5.5%
120	1.4%	0.1%	1.3%	2.0%	0.0%	1.9%
180	0.6%	0.0%	0.6%	0.9%	0.0%	0.9%
240	0.3%	0.0%	0.3%	0.5%	0.0%	0.5%
Mean survival[a]	15.76	8.68	7.08	17.73	8.37	9.36

[a]Mean survival in months, based on a 20 year time horizon

Figure 1: Full parametric approach to predict OS; based on Log-normal distribution

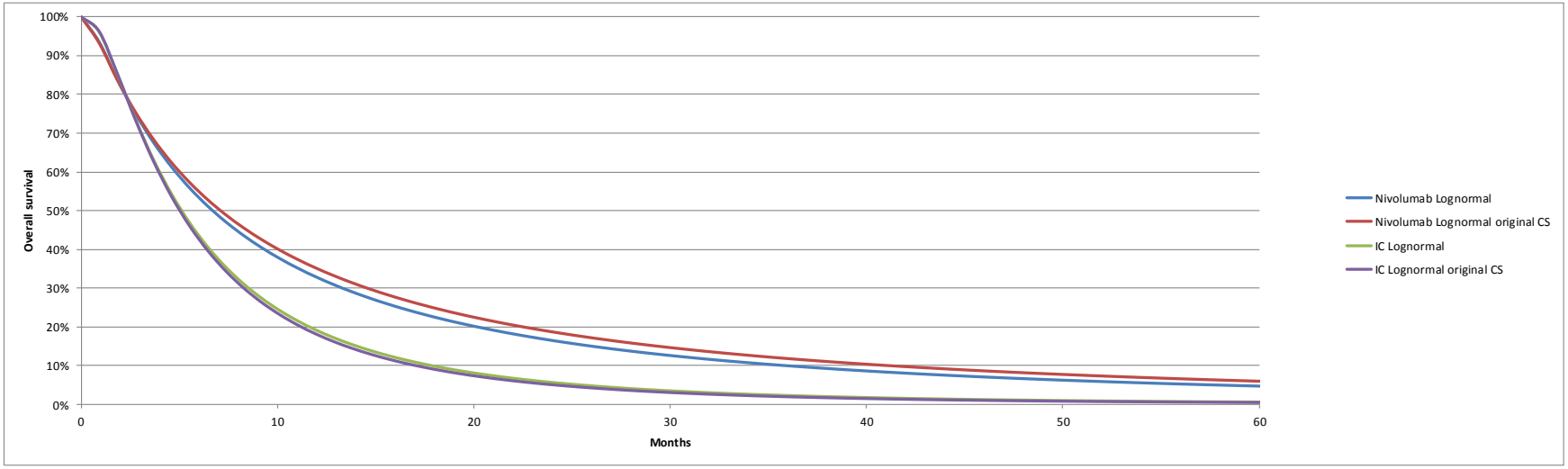

Table 2: Piecewise approach to predict OS; based Kaplan-Meier curves (first phase) and Exponential distribution (second phase)

	Nivolumab	IC	Difference	Nivolumab	IC	Difference	Nivolumab	IC	Difference	Nivolumab	IC	Difference
Cut-off	**20 weeks**			**28 weeks**			**36 weeks**			**48 weeks**		
Months	**OS**											
12	34.4%	19.4%	14.9%	34.7%	19.5%	15.2%	33.9%	19.7%	14.2%	33.1%	18.0%	15.1%
24	13.0%	3.8%	9.2%	12.3%	4.2%	8.0%	13.3%	4.1%	9.1%	14.1%	5.7%	8.4%
36	4.9%	0.7%	4.2%	4.3%	0.9%	3.4%	5.2%	0.9%	4.3%	6.0%	1.8%	4.2%
48	1.9%	0.1%	1.7%	1.5%	0.2%	1.3%	2.0%	0.2%	1.8%	2.6%	0.6%	2.0%
60	0.7%	0.0%	0.7%	0.5%	0.0%	0.5%	0.8%	0.0%	0.8%	1.1%	0.2%	0.9%
120	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
180	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
240	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Mean survival[a]	11.84	8.04	3.80	11.66	8.10	3.56	11.92	8.09	3.83	12.20	8.38	3.82

[a]Mean survival in months, based on a 20 year time horizon

Figure 2: <u>Piecewise approach to predict OS; based Kaplan-Meier curves (first phase) and Exponential distribution (second phase)</u>

Table 3: Piecewise approach to predict OS; based Kaplan-Meier curves (first phase) and Log-normal distribution (second phase)

	Nivolumab	IC	Difference	Nivolumab	IC	Difference	Nivolumab	IC	Difference
Cut-off	**20 weeks**			**36 weeks**			**48 weeks**		
Months	**OS**								
12	32.7%	18.6%	14.2%	31.9%	17.5%	14.4%	34.1%	18.8%	15.4%
24	16.7%	7.5%	9.2%	16.6%	7.4%	9.2%	14.1%	5.5%	8.7%
36	10.5%	4.2%	6.4%	11.2%	4.5%	6.6%	7.8%	2.4%	5.4%
48	7.3%	2.6%	4.7%	8.3%	3.2%	5.1%	5.0%	1.3%	3.6%
60	5.4%	1.8%	3.6%	6.5%	2.4%	4.1%	3.4%	0.8%	2.6%
120	1.9%	0.5%	1.4%	2.8%	0.9%	1.9%	0.9%	0.2%	0.8%
180	0.9%	0.2%	0.7%	1.7%	0.5%	1.2%	0.4%	0.0%	0.4%
240	0.5%	0.1%	0.4%	1.1%	0.3%	0.8%	0.2%	0.0%	0.2%
Mean survival[a]	16.80	10.07	6.73	18.55	10.82	7.73	14.33	8.83	5.51

[a]Mean survival in months, based on a 20 year time horizon

Figure 3: Piecewise approach to predict OS; based Kaplan-Meier curves (first phase) and Log-normal distribution (second phase)

Table 4: Health state utilities estimated using the mixed model

Health state	Nivolumab	IC	Average (used as treatment independent utility value)
	Mean utility value (95% CI)	Mean utility value (95% CI)	Mean utility value
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

Table 5: ERG base-case and requested additional scenario analyses (with PAS for nivolumab)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
ERG Base-case							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,459	0.67	0.36	[redacted]	0.52	[redacted]	£47,419
Paclitaxel	11,859	0.67	0.36	[redacted]	0.52	[redacted]	£44,007
Methotrexate	11,525	0.67	0.36	[redacted]	0.52	[redacted]	£44,820
Scenario: using piecewise approach to predict OS; based Kaplan-Meier curves (first phase) and Exponential distribution (second phase)							
Cut-off point: 20 weeks							
Nivolumab	[redacted]	0.93	[redacted]				
Docetaxel	10,358	0.63	0.34	[redacted]	0.30	[redacted]	£72,037
Paclitaxel	11,758	0.63	0.34	[redacted]	0.30	[redacted]	£66,727
Methotrexate	11,424	0.63	0.34	[redacted]	0.30	[redacted]	£67,993
Cut-off point: 28 weeks							
Nivolumab	[redacted]	0.92	[redacted]				
Docetaxel	10,366	0.63	0.34	[redacted]	0.29	[redacted]	£74,885
Paclitaxel	11,766	0.63	0.34	[redacted]	0.29	[redacted]	£69,355
Methotrexate	11,432	0.63	0.34	[redacted]	0.29	[redacted]	£70,674
Cut-off point: 36 weeks							
Nivolumab	[redacted]	0.94	[redacted]				
Docetaxel	10,365	0.63	0.34	[redacted]	0.31	[redacted]	£71,567
Paclitaxel	11,765	0.63	0.34	[redacted]	0.31	[redacted]	£66,293
Methotrexate	11,431	0.63	0.34	[redacted]	0.31	[redacted]	£67,551

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cut-off point: 48 weeks							
Nivolumab	[redacted]	0.96	[redacted]				
Docetaxel	10,413	0.65	0.35	[redacted]	0.30	[redacted]	£70,849
Paclitaxel	11,813	0.65	0.35	[redacted]	0.30	[redacted]	£65,628
Methotrexate	11,479	0.65	0.35	[redacted]	0.30	[redacted]	£66,872
Scenario: using a disutility of 0.149 (difference in post progression utility between nivolumab and IC) for patients that discontinued nivolumab treatment							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,459	0.67	0.36	[redacted]	0.52	[redacted]	£66,560
Paclitaxel	11,859	0.67	0.36	[redacted]	0.52	[redacted]	£61,770
Methotrexate	11,525	0.67	0.36	[redacted]	0.52	[redacted]	£62,912

IC: investigator choice; ICER: incremental cost-effectiveness; QALYs quality adjusted life-years

Response from clinical expert, Professor Kevin Harrington

1. Could you please comment on the plausibility of the company's assumption that the majority of patients who have not progressed will discontinue treatment? Are there reasons that could make patients discontinue treatment before progression? If so, what proportion of patients are likely to discontinue for reasons other than progression.
I believe that the company's assumptions are entirely plausible, indeed probably rather conservative. I my experience, chronic administration of biological agents such as monoclonal antibodies becomes increasingly onerous and unpopular with patients. We have a number of head and neck cancer patients approaching the 2-year mark of single-agent anti-PD1 therapy on a different trial and they are eagerly anticipating the 2-year time point when the protocol states that they will discontinue therapy. The main issues are that, by this point in a patient's treatment, he or she is likely to have stabilised with a response or radiological "stable disease" (we suspect that some of these patients simply have residual fibrotic masses). Motivation to continue chronic attendance at hospital for intravenous therapy diminishes at this point. I doubt that discontinuations at this point will be due to toxicities. It is also becoming increasingly well understood (from the melanoma and lung data) that patients who discontinue therapy at 18-24 months are very likely to remain in remission and, even if they do relapse, they tend to respond again to PD1 inhibition. Therefore, it seems plausible that patients who discontinue at (or before) 2 years will not experience a detriment in effect of therapy.
That view is gaining increasing traction with clinicians but is, as yet, largely based on word-of-mouth.

2. Could you please comment on the appropriateness and plausibility of the survival estimates predicted by the different modelling approaches.
It is important to emphasise that I am not an expert in the mathematical modelling of survival (especially in the context of trying to make suture predictions of patients outcomes).
To my mind, the emerging data from a range of tumour types including head and neck cancers, demonstrate a plateau in the survival curve. I agree that modelling SCC head and neck using similar lung cancer data from a similar histology seems a reasonable approach. The data provided by the company using the log-normal methodology appear to estimate a plateau around the level that appears (to me) to be a reasonable estimate of what we might expect in SCC head and neck. The data provided by the ERG did not include modelled curves, so I found it difficult to see whether or not a plateau was generated using their piece-wise approach.
In my view, any estimate of likely survival should include a long-term, durable plateau around 7-15%.

3. Could you please comment on the plausibility of the relatively high utility value for nivolumab in the postprogression health state compared with that in the progression-free state and also compared with that of the comparator arm in the post-progression state.
Again, I must emphasise that I am not an expert in health economics or in the calculation and interpretation of utility values.

However, the data that I presented at ESMO in October 2016 (on patient-reported outcomes PROs) supports the observation that patients treated with nivolumab maintain PROs. This observation includes patients whose disease has progressed and who are in the post-treatment state. In contrast, the data on the IC comparator arm showed a progressive deterioration at the 9 and 15 week period (indeed, the deterioration appeared to be accentuated at the later time point - when the majority of IC-treated patients were post-progression).

4. Could you please comment on the plausibility of assuming that the health benefit with nivolumab is constant and will be maintained up to 5 years or 10 years. Would you expect to see some decline in the benefits after treatment ceases before 5 years? Would this apply to Quality of life benefits as well?

I am not confident that we have sufficient data at present to make certain predictions on this matter. I believe that the majority of patients who enter the plateau phase will continue to enjoy the health benefits of nivolumab long-term (including out to 5-10 years). It is important to recognise that we have NEVER been in a situation where we could even contemplate patients with relapsed/metastatic SCC head and neck living for 5-10 years. However, it is also highly likely that a proportion (precise number is impossible to state) will experience disease recurrence. These patients may well respond to further treatment, but some are likely to die of disease. I do not think that I am able to make accurate projections of the numbers in each group.

I hope that these answers are of some use to the committee

best wishes

Kevin

Professor K.J. Harrington PhD FRCP FRCR
[redacted]
[redacted]

Response from clinical expert, Dr Anthony Kong

Could you please comment on the plausibility of the company's assumption that the majority of patients who have not progressed will discontinue treatment? Are there reasons that could make patients discontinue treatment before progression? If so, what proportion of patients are likely to discontinue for reasons other than progression.

As stated in the company's document, the optimum duration of nivolumab is uncertain. However, the risk of developing side effects increases with prolonged treatment. Data has shown that some patients can continue to derive the benefit from the treatment long after stopping treatments. In the study by Gettinger L et al (2015), it was reported that NSCLC patients received nivolumab up to 96 weeks and eighteen responding patients discontinued nivolumab for reasons other than progressive disease. Nine (50%) of those had responses lasting 9 months after their last dose. There were 14% of patients with grade 3 to 4 treatment-related adverse events and 2% (three) patients with treatment-related deaths, each associated with pneumonitis.

For SCCHN, immunotherapy is new and most of our experience is from clinical trials. Currently I have two patients on HAWK and CONDOR trials, who had excellent clinical responses and almost no or few side effects from the treatments, had stopped immunotherapy after 1 year as part of the protocol. I was initially very nervous in stopping their therapies. However, the recent scans (three months after they stopped treatment) have continued to show sustained response. As part of the protocol, they can go back to the treatment if they progress again.

So I think the reasons for stopping the treatment other than disease progression could be company's recommendation for the drugs (or as part of the protocol), patient preference, side effects, physicians' recommendation.

One thing that needs to ask the company: for example in HAWK and CONDOR protocols, patients were only offered treatment for 1 year but can go back to treatment if progresses as part of the protocol. What is uncertain is whether the patients will derive benefit again if go back to nivolumab after disease progression while nivolumab is stopped and whether the stopping and restarting the immunotherapy for patients, needs to take into account for cost-effective analysis.

Could you please comment on the appropriateness and plausibility of the survival estimates predicted by the different modelling approaches.

Currently the survival data of PD1 antibodies from HNSCC patients is not long enough to provide a definite conclusion on long-term outcome. However, data from melanoma and lung cancers (CheckMate 003) have shown that a small proportion of patients can survive long-term and the survival curve can plateau for a small proportion of patients. Therefore, it is possible that the revised base case lognormal model can underestimate long-term survival for a small proportion of patients as stated by the company.

Therefore, I agree with the company's responses and with the ERG in their assessment of the original Company Evidence Submission: "the ERG considered the statistical methods used by the company for selecting the distributions for the time-to event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis".

Could you please comment on the plausibility of the relatively high utility value for nivolumab in the post-progression health state compared with that in the progression-free state and also compared with that of the comparator arm in the post-progression state.

There is still much we need to learn from immunotherapy. We know that a small proportion of patients can derive benefit from immunotherapy if treated beyond progression based on RECIST criteria (George S et al. JAMA Oncol. 2016;2(9):1179-1186) In addition, immunotherapy can have synergistic or additive with other treatments such as radiotherapy, chemotherapy, targeted therapies, either concurrently or sequentially. Therefore, post-progression from immunotherapy, it is possible that some patients may derive more benefit from subsequent therapies, be it chemotherapy or targeted therapy. In addition, some patients who have excellent partial response from immunotherapy with a much reduction of disease burden, can remain well for a prolonged period of time if only have progression in a limited sites of disease. For example, I had a patient who had excellent partial responses to immunotherapy, had to stop treatment due to side effects. He hasn't had treatment for several months and majority of the disease burden remains controlled although one new lymph node has started to grow but not causing his much problem. Therefore, I think the higher utility value in the post-progression health state is possible. Although one also needs to take account of the possible deterioration in quality of life and morbidities due to possible side effects from the immunotherapy treatment.

Could you please comment on the plausibility of assuming that the health benefit with nivolumab is constant and will be maintained up to 5 years or 10 years. Would you expect to see some decline in the benefits after treatment ceases before 5 years? Would this apply to Quality of life benefits as well?

Certainly, data from lung and melanoma patients have suggested that a small proportion of patients can have long-term survival with good health and maintain the health benefit with nivolumab. However, I do think that with longer duration of follow-up more patients will start to progress and the number of patients who maintain health benefit will drop but there may remain a very small number of patients who may continue to derive health benefit with nivolumab for a prolonged period. I will be very surprised of any recurrent or metastatic HNSCC patients who will last beyond 5 years as this is not usually possible with conventional treatment and I am not truly convinced that this will be the case with immunotherapy for this group of patients without seeing the data from SCCHN. What is unknown is whether those responded patients who have previously stopped treatment can derive benefit again after being rechallenged with the drug and whether this will prolong their survival further.