NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (CDF Review of TA490) [ID1585]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (CDF Review of TA490) [ID1585]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Bristol-Myers Squibb

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   - **a.** Head and Neck Cancer UK (HANCUK)
   - **b.** The Swallows Head and Neck Cancer Charity

4. **Expert personal perspectives** from:
   - a. Andrew Sykes, Consultant Clinical Oncologist – clinical expert, nominated by Bristol-Myers Squibb
   - b. Christopher Curtis, Chief Executive Officer – patient expert, nominated by The Swallows Head and Neck Cancer Charity

5. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

6. **Evidence Review Group report – factual accuracy check**

7. **Public Health England Study Report**

8. **Technical report**

9. **Technical engagement response from company**

There were no technical engagement responses received from consultees and commentators or the invited experts.

10. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA490

Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (CDF review of TA490) [ID1585]

Company evidence submission for committee

February 2020

File name	Version	Contains confidential information	Date
ID1595_CDF Review of TA490_ACIC	1.0	Yes	27/02/2020

Instructions for companies

This is the template you should use for your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the Cancer Drugs Fund (CDF) review process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission should not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted.

Provide supportive and detailed methodological or investigative evidence in an appendix to this submission.

When cross referring to evidence in the original submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Cancer Drugs Fund review submission

A.1 Background

Nivolumab is recommended for use within the Cancer Drugs Fund (CDF) as an option for treating squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy, only if:

- The disease has progressed within 6 months of having chemotherapy
- Nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression and
- The conditions in the managed access agreement are followed.

The clinical-effectiveness evidence for nivolumab was taken from the CheckMate 141 trial, a phase III randomised controlled trial comparing nivolumab with the investigator's choice (IC) of therapy.

The committee concluded that based on a Patient Access Scheme (PAS) of [redacted] and its preferred assumptions the most plausible ICER was between £45,000 and £73,600 per quality-adjusted life year (QALY) (dependent on the time point for extrapolation and treatment-dependent/independent utility values) for the full trial population, irrespective of programmed death ligand 1 (PD-L1) expression. The company subsequently proposed a [redacted] commercial access agreement to include nivolumab in the CDF for all patients irrespective of PD-L1 expression. The committee noted that the company's proposal included a 2-year stopping rule for nivolumab treatment. Although it had previously concluded that it would not consider a stopping rule for routine commissioning, the committee accepted that it would be reasonable to manage access while in the CDF.

The committee noted that the ICERs for the full trial population using the commercial access agreement were between £30,377 and £49,408 per QALY gained depending on the time point used for extrapolation and utility values chosen (see Table 1). It therefore concluded that nivolumab showed plausible potential for being cost effective for the full trial population, incorporating a 2-year stopping rule and with the commercial access agreement.

Table 1: Cost-effectiveness estimates with the proposed CDF price and a 2-year stopping rule from original appraisal

Population	Utilities	Incremental cost-effectiveness ratio (nivolumab versus docetaxel)		
		20 weeks cut-point	36 weeks cut-point	48 weeks cut-point
All comers	Treatment-specific	£33,656	£30,377	£39,226
	Treatment-independent	£42,881	£38,632	£49,408

Areas of uncertainty

The committee noted that the long-term overall survival (OS) estimates from the trial were uncertain, which could be resolved with further data collection. It further concluded that it is plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression. The potential impact of PD-L1 expression level was included as part of the data collection arrangement.

The utility values were also associated with significant uncertainty. Further data collection of utility values was not included as part of the data collection agreement, however, the committee noted they would welcome any new evidence on utility values if available.

Data collection

The data collection agreement specifies the terms of data collection during the period of managed access. In summary:

- The pivotal clinical-effectiveness evidence for nivolumab compared with IC was taken from the CheckMate 141 trial. This trial is the primary source for data collection under the managed access agreement. 4-year follow-up data would be undertaken based on the trial protocol including the reporting of OS, treatment duration and subgroup analysis by PD-L1 expression level. The company will provide updated evidence on the CheckMate 141 trial.
- Observational data will also be collected for nivolumab during the period of managed access via the systemic anti-cancer therapy (SACT) dataset to support the data collected in the clinical trial. SACT will collect data on OS, duration of therapy and PD-L1 expression. Public Health England will provide a summary of the observational data collected.

Updated analysis

As seen in the updated analysis presented in this document, the ERG and Committee were over-conservative during the initial appraisal. The new, long-term data demonstrate that nivolumab is cost-effective and should be funded through routine commissioning.

A.2 Key committee assumptions

Table 2 presents the key committee assumptions as set out in the terms of engagement, which have been adhered to in this submission. In addition to using the committee-preferred assumptions, in light of the newly available data for nivolumab, relevant assumptions have been explored and scenario analyses incorporating these have been presented, where appropriate.

Table 2: Key committee assumptions as set out in the terms of engagement

Area	Committee preferred assumptions
Population	• The committee noted that the trial included adults with recurrent or metastatic SCCHN that progressed within 6 months of platinum-based therapy, in either the early or locally advanced disease stage. • After the committee reviewed the EPAR and heard from clinical experts, it concluded that its recommendation would focus on the population represented in the trial because this underpins the marketing authorisation and is a distinct subset of the population whose disease has progressed after platinum-based chemotherapy. **The CDF review will focus on this population only**
Comparators	• Docetaxel is the most appropriate comparator for people fit enough to have docetaxel. • Methotrexate is normally reserved for people who have a poor performance status and are not fit enough to have a taxane, or as subsequent therapy for people who have had a taxane. • The committee concluded that it is valid to assume that docetaxel and paclitaxel are equivalent, but it was not persuaded by the company's assumption that docetaxel is equivalent to methotrexate. **Docetaxel is the comparator of interest in the CDF review**

Generalisability of CheckMate 141	• There is some uncertainty about the relevance of CheckMate 141 to UK practice because cetuximab was used as one of the comparators in the trial. • However, the committee concluded that although there are some differences between the trial population and the UK population, **the CheckMate 141 results are relevant to the UK population**
Overall survival	• The committee concluded that there was significant improvement in OS in the nivolumab group at 18-month follow up, but the incremental OS benefit beyond 24 months is uncertain. • The committee considered that the uncertainties about the OS benefit beyond 2 years could be addressed by collecting longer follow-up survival data from CheckMate 141. **The committee are expecting updated overall survival evidence from CheckMate 141**
Subgroup analysis: PD-L1 expression	• The committee concluded that there is evidence of nivolumab's benefit in those with a PD-L1 expression of 1% or more, but for those with a PD-L1 expression of less than 1% the benefit is much less convincing. • The committee specifically stated that the longer follow-up survival data from CheckMate 141 should be collected according to levels of PD-L1 expression. • The committee stressed the importance of collecting prevalence and outcome data by PD-L1 expression, stating that any recommendation for the full trial population would depend on a clear commitment from the company to collect these data. **The committee are expecting the updated overall survival evidence from CheckMate 141 to include analysis by PD-L1 expression**
Model structure	• The company's model structure is suitable for decision making. **It is anticipated that the model structure will not change for the CDF review**
Extrapolation of survival	• The piecewise model is preferred for extrapolating survival, that is, using the observed Kaplan-Meier data, then fitting an appropriate distribution at a reasonable time point. • The log normal distribution was the only distribution explored by the company. The committee expressed concerns about the long tails associated with the lognormal distribution. However, because no other distributions were explored, the committee accepted the company's piecewise lognormal model. • Three different time points to extrapolate from were explored that is, 20, 36 and 48 weeks. The committee noted the inconsistent effect the time points has on the cost effectiveness and concluded the most appropriate time point to extrapolate the trial data is uncertain. • The modelled progression-free survival and time-to-treatment discontinuation was uncertain as it did not fit the parametric distributions well. **A piecewise model is expected to be used for extrapolation of overall survival in the CDF review**

	It is anticipated that the timepoint to extrapolate from and the distribution will be explored in the CDF review
Long-term treatment effect	• Continued treatment benefit up to 5 years is plausible, but assuming constant benefit after treatment stops is uncertain. **Continued benefit should be reviewed in light of any new evidence**
Utilities	• The committee was concerned that the utility values calculated by the company's mixed model approach were associated with significant uncertainty. • The most appropriate utility values lie between the treatment-dependent and the treatment-independent estimates. **Quality-of-life benefit cannot be assumed to remain constant** **Exploration of the most appropriate utility values should be reviewed in light of any new evidence**
Stopping rule	• The committee considered analyses without a stopping rule are more appropriate for decision-making • Given the uncertainty about the stopping rule, the committee concluded that it would only consider analyses with the stopping rule in the context of potential inclusion in the CDF, as an approach to managing risk **The appropriateness of a 2-year stopping should be reviewed in light of any new evidence**
End of life	• Nivolumab meets the end-of-life criteria
Cost savings from other indications	• Accounting for cost savings from other indications is not appropriate **These benefits are not expected to be included**
ERG's amendments to the company's model	• Adding the cost and disutility for pneumonitis and using treatment-independent proportions for subsequent treatment **It is anticipated that the ERG amendments will be included**

Abbreviations: CDF: Cancer Drugs Fund; EPAR: European public assessment report; ERG: Evidence Review Group; OS: overall survival; PD-L1: programmed death ligand 1; SCCHN: squamous cell carcinoma of the head and neck.

A.3 Other agreed changes

The company have not altered the decision problem, submitted additional evidence, or made further alterations to the model during the CDF review period except those agreed by NICE in advance.

A.4 The technology

Information about the technology being reviewed is presented in Table 3. Since the original submission for TA490, the licensed dose of nivolumab has been updated to a flat dose of 240 mg every two weeks (Q2W), rather than the weight-based dose used in the CheckMate 141 trial (3 mg/kg every 2 weeks).[1] The flat dose approximates the exposures achieved with 3 mg/kg in patients weighing 80 kg, the median body weight of patients across nivolumab trials. Nivolumab flat-dosing regimens are supported by clinical safety data and population pharmacokinetic modelling across many indications, which demonstrated that distributions of nivolumab exposures after 3 mg/kg Q2W and 240 mg Q2W were similar and below the exposures observed

with 10 mg/kg Q2W. No clinically meaningful relationship between body weight or nivolumab exposure or nivolumab exposure quartiles and frequency or severity of adverse events was observed. Based on consistent exposure-response relationships across indications, the benefit-risk profile of nivolumab 240 mg Q2W is likely to be similar to 3 mg/kg Q2W, therefore the clinical effectiveness of nivolumab that was demonstrated in CheckMate 141 (weight-based dose) is expected to be generalisable to the use of nivolumab in clinical practice (flat dose).

Table 3: Technology being reviewed

UK approved name and brand name	Nivolumab (Opdivo®)
Mechanism of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[2]
Marketing authorisation/CE mark status	For the indication of interest for this submission, positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was received on 23rd March 2017, and marketing authorisation was granted on 28th April 2017.[1, 3]
Indications and any restriction(s) as described in the summary of product characteristics	The EU marketing authorisation wording for nivolumab monotherapy in the indication of interest for this submission is: *"Nivolumab monotherapy for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) in adults progressing on or after platinum-based therapy"*[2] Nivolumab monotherapy is currently licensed for the following indications:[2] • For the treatment of advanced (unresectable or metastatic) melanoma in adults • For the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection • For the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults • For the treatment of advanced RCC after prior therapy in adults • For the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin • For the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy
Method of administration and dosage	Nivolumab is administered via intravenous infusion, over 30 minutes. The recommended dosage of nivolumab in this indication is 240 mg flat dose every two weeks.[2] This is different to the weight-based dose of 3 mg/kg that was recommended at the time of the original NICE appraisal

<table>
<tr><td></td><td>for nivolumab in this indication. The change in recommended dosage was introduced on 23rd April 2018.[1]
Treatment to be continued as long as clinical benefit is observed or until treatment is no longer tolerated.
Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab or nivolumab in combination with ipilimumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.</td></tr>
<tr><td>Additional tests or investigations</td><td>There are no additional tests or investigations required for nivolumab.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>Acquisition cost (excluding VAT):[4]
<table>
<tr><th>Vial size:</th><th>40mg/4ml</th><th>100 mg/10 ml</th><th>240 mg/40 ml</th></tr>
<tr><td>List price:</td><td>£439.00</td><td>£1,097.00</td><td>£2,633.00</td></tr>
<tr><td>PAS price:</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
The average cost of nivolumab (fixed dose) estimated based on the revised economic analyses: £23,076 (with nivolumab at list price) and £[redacted] (with nivolumab at PAS price).</td></tr>
<tr><td>Commercial arrangement (if applicable)</td><td>A simple PAS representing a [redacted] discount has been approved for nivolumab.</td></tr>
<tr><td>Date technology was recommended for use in the CDF</td><td>November, 2017</td></tr>
<tr><td>Data collection end date</td><td>September, 2019</td></tr>
</table>

Abbreviations: ASCT: autologous stem cell transplant; CDF: Cancer Drugs Fund; CHMP: Committee for Medicinal Products for Human Use; HuMAb: human monoclonal antibody; IgG4: immunoglobulin G4; NICE: The National Institute for Health and Care Excellence; NSCLC: non-small-cell lung cancer; PAS: Patient Access Scheme; PD-1: programmed death-1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2; RCC: renal cell carcinoma; R/M SCCHN: recurrent/metastatic squamous cell carcinoma of the head and neck; VAT: Value Added Tax.

A.5 Clinical effectiveness evidence

The CheckMate 141 trial is the primary source of clinical effectiveness evidence for this submission, with supportive evidence provided by the SACT data cohort study. A summary of these sources of clinical effectiveness evidence is presented in Table 4.

CheckMate 141 enrolled adult patients with recurrent and/or metastatic (R/M) squamous cell cancer of the head and neck (SCCHN) who progressed within 6 months after platinum-based therapy. A total of 361 patients were randomised (referred to hereafter as the overall population) and 260 (72.0%) patients had quantifiable PD-L1 expression at baseline.[5] Of these 260 patients, 149 patients (57.3%) had PD-L1 expression ≥1% and 111 patients (42.7%) had PD-L1 expression <1%.[5] Since the original submission for TA490, data from the latest data cut of the CheckMate 141 trial (4-year; 15th October 2019) have become available. This data cut provides data from a minimum follow-up of 48.2 months (representing 36.8 additional months of follow-up). At the time of this data cut-off, thirteen patients in the nivolumab arm and one patient in the IC arm were still alive and in follow-up, with [redacted].[6]

Given the maturity of the data available from the latest data cut-off of CheckMate 141 (15th October 2019), the evidence presented in this submission addresses the committee's key areas of uncertainty regarding long-term survival and clinical effectiveness. Outcomes from CheckMate 141 that are of relevance to this appraisal are time to treatment discontinuation (TTD), OS and PFS and these are presented in Section A.6.1, including a summary of outcomes by PD-L1 subgroups. Further analyses of EQ-5D data from the original data cut-off of the CheckMate 141 trial presented at CDF entry (20th September 2016) have also been conducted in order to address the concerns raised in TA490 about utility remaining constant over time in the economic model. Specifically, the change in utility that patients experience as they near death has been analysed to explore the extent to which utility may diminish over time (see Sections A.6.1 and A.8.3).

The generalisability of outcomes from the CheckMate 141 trial is supported by evidence from the SACT data cohort, which provides data for the efficacy of nivolumab in 296 UK patients treated in routine clinical practice (see Section A.6.2 for a comparison of outcomes between the SACT cohort and CheckMate 141 trial; full details of the SACT cohort are provided in the report produced by Public Health England and are not replicated here).[7] Data from the SACT cohort were not included in the economic model because the study follow-up was less than that of CheckMate 141, and therefore does not address the committee's key area of uncertainty regarding long-term survival. However, evidence from the SACT data cohort is based on UK clinical practice, and therefore supports the generalisability of Checkmate-141 to the real-world setting.

Table 4: Sources of clinical effectiveness evidence

Study title	CheckMate 141 (NCT02105636) – Primary evidence source	SACT data cohort study – Supportive evidence
Study design	Multicentre, open-label, phase III randomised controlled trial	SACT data cohort study
Population	**Key inclusion criteria:** • Males and females ≥18 years of age with an Eastern Cooperative Oncology Group (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[8] • 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	**Eligibility criteria for nivolumab use in the CDF:** • Patient has a confirmed histological diagnosis of squamous cell carcinoma of the head and neck • Patient has recurrent or metastatic head and neck cancer that is not amenable to local therapy with curative intent (surgery and/or radiation therapy with or without chemotherapy) • Patient's disease has progressed during or within 6 months of the last dose of platinum-based chemotherapy • Patient has an ECOG performance status of 0 or 1 and would otherwise be potentially fit for docetaxel-based or methotrexate-based second-line chemotherapy • Patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody • That every effort has been made for the patient to have PD-L1 testing with an approved and validated test to determine the Tumour Proportion Score (TPS)

	A full list of inclusion and exclusion criteria is presented in Appendix A	
Intervention(s)	Nivolumab (3 mg/kg, i.v. infusion, Q2W)	Nivolumab (i.v. infusion, Q2W)
Comparator(s)	Investigator's choice of chemotherapy: • 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)	Not applicable
Outcomes collected that address committee's key uncertainties (outcomes in **bold** have been included in the cost-effectiveness model)	**Overall population:** • **Time to treatment discontinuation (TTD)** • **Progression-free survival (PFS)** • **Overall survival (OS)** **PD-L1 subgroups (≥1% or <1%):** • **Time to treatment discontinuation (TTD)** • **Progression-free survival (PFS)** • **Overall survival (OS)** **EQ-5D data from the CheckMate 141 trial have also been reanalysed**	• Time to treatment discontinuation (TTD) • Overall survival (OS) (overall population and by PD-L1 status)
Reference to section in appendix	Not applicable, all clinical effectiveness results have been presented in the submission	

Abbreviations: CT: computerized tomography; CTLA-4: cytotoxic T-lymphocyte-associated antigen-4; ECOG: Eastern Cooperative Oncology Group; i.v.: intravenous infusion; MRI: magnetic resonance imaging; OS: overall survival; PD-1: programmed death-1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2; PFS: progression-free survival; QW: weekly; Q2W: once every 2 weeks; RECIST: Response Evaluation Criteria in Solid Tumours; R/M SCCHN: recurrent/metastatic squamous cell carcinoma of the head and neck; SACT: systemic anti-cancer therapy; SCC: squamous cell carcinoma; TPS: Tumour Proportion Score; TTD: time to treatment discontinuation.
Source: Ferris *et al.* (2016)[9] and Public Health England report[7]

A.6 Key results of the data collection

A.6.1 *CheckMate 141 (NCT02105636)*

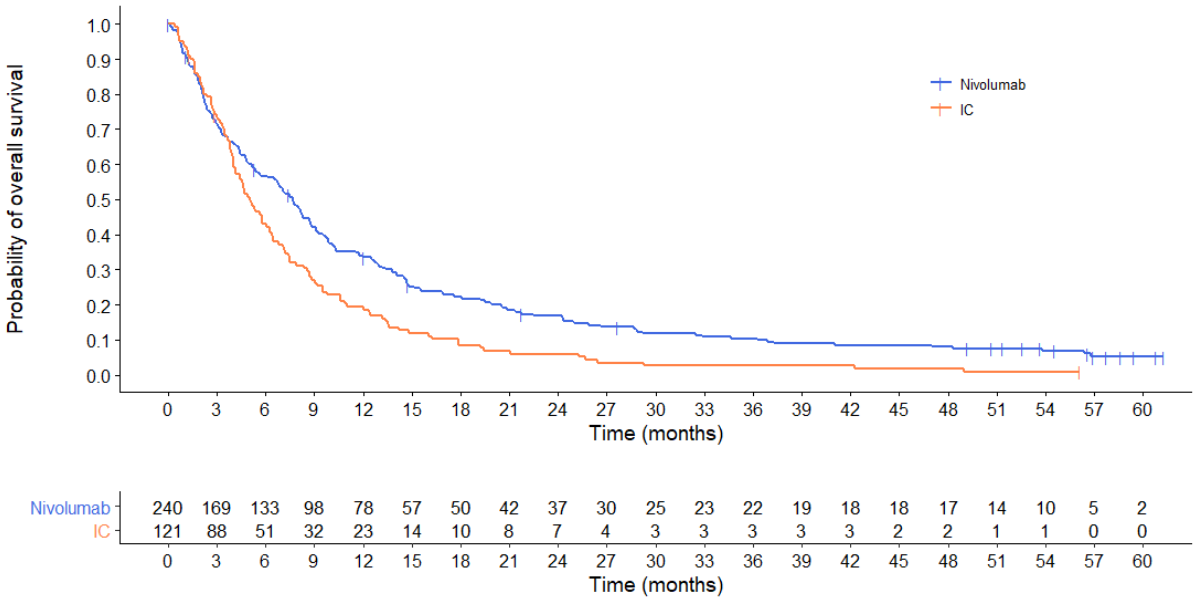
Results from the overall population

The results from the latest data cut of the CheckMate 141 trial (15th October 2019) (OS, PFS and TTD) are generally consistent with those presented in the original appraisal and provide long-term evidence to support the benefit of nivolumab versus IC for patients with R/M SCCHN after platinum-based therapy.

Overall survival

One of the key uncertainties in the original appraisal was the long-term survival benefit associated with nivolumab. A summary of OS from the latest data cut of the CheckMate 141 trial (15th October 2019) is presented in Table 5 for the overall population, alongside the original data cut-off presented at CDF entry (20th September 2016). The Kaplan-Meier plot of OS for the overall population from the latest data cut is presented in Figure 1. As shown in Table 5, the survival rates (up to 48 months) in the nivolumab arm were consistently higher than IC at the time of the latest data cut of the CheckMate 141 trial, with the 48-month survival rate for nivolumab being four times higher than that of the IC arm. The survival benefit associated with nivolumab can also be seen in the Kaplan-Meier curves, which show a continued benefit for patients in the nivolumab treatment arm versus IC from 6 months onwards. These additional data from the latest data cut of the CheckMate 141 trial clearly demonstrate that treatment with nivolumab is associated with a long-term OS benefit compared to IC.

Figure 1: Kaplan-Meier plot of overall survival in the overall population in CheckMate 141



Data cut-off: 15th October 2019
Abbreviations: IC: investigator's choice.
Source: CheckMate 141 Data on File (15th October 2019)[6]

Table 5: Summary of overall survival – overall population

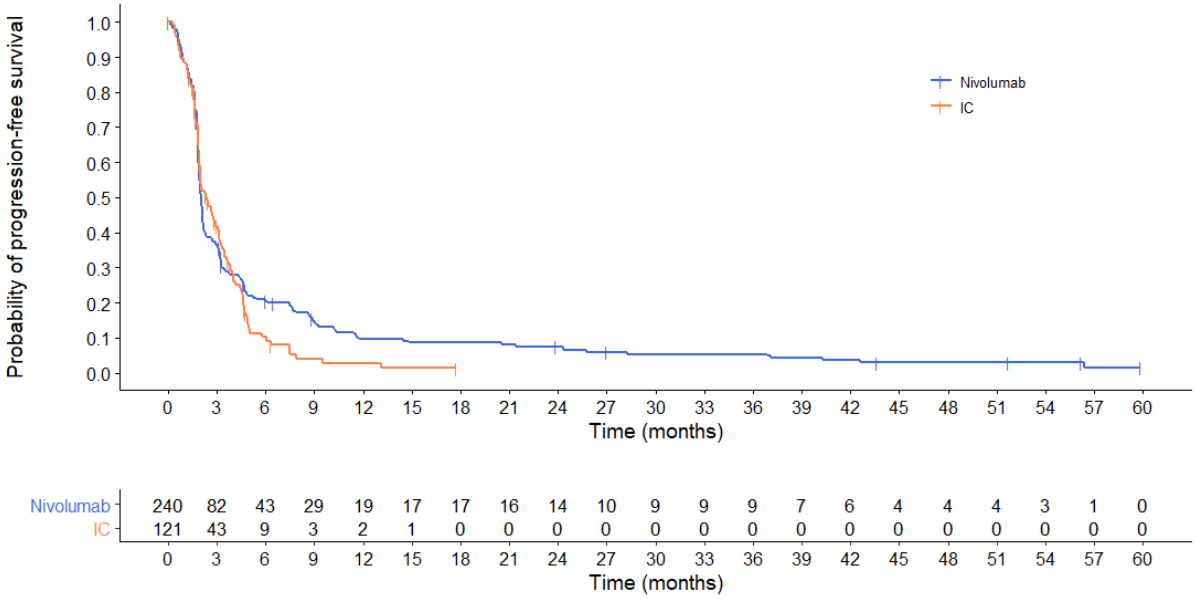
Outcome	Data cut-off: 20th September 2016		Data cut-off: 15th October 2019	
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)
Deaths, n/N (%)	[redacted]	[redacted]	218/240 (90.8)	118/121 (97.5)
Median OS, months (95% CI)	[redacted]	[redacted]	7.72 (5.68, 8.74)	5.06 (4.04, 6.24)
12-month survival rate, % (95% CI)	[redacted]	[redacted]	33.4 (27.5, 39.5)	19.4 (12.9, 26.9)
18-month survival rate, % (95% CI)	[redacted]	[redacted]	22.1 (17.0, 27.6)	8.4 (4.3, 14.3)
24-month survival rate, % (95% CI)	[redacted]	[redacted]	16.8 (12.3, 21.9)	5.9 (2.6, 11.1)
36-month survival rate, % (95% CI)	[redacted]	[redacted]	10.3 (6.8, 14.7)	2.5 (0.7, 6.6)
48-month survival rate, % (95% CI)	[redacted]	[redacted]	8.0 (4.9, 12.0)	1.7 (0.3, 5.4)

Abbreviations: CI: confidence interval; HR: hazard ratio; IC: investigator's choice; NA: not applicable; OS: overall survival.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Figure 6.1-1 & Table 6.1-1;[10] CheckMate 141 Data on File (15th October 2019)[6]

Progression-free survival

A summary of PFS from the latest data cut of the CheckMate 141 trial (15th October 2019) is presented in Table 6 for the overall population, alongside the original data cut-off presented at CDF entry (20th September 2016). The Kaplan-Meier plot of PFS for the overall population from the latest data cut is presented in Figure 2. As per the original submission, although median PFS was less prolonged in the nivolumab arm (2.04 months [95% CI, 1.91, 2.14] for nivolumab versus 2.33 months [95% CI, 1.94, 3.06] for IC), the overall HR for disease progression or death favoured nivolumab (0.82; 95% CI, 0.65, 1.02; p=0.0766). As shown in Figure 2, 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 (20.4 months [95% CI, 15.4, 26.0]) compared to the IC arm (10.2 months [95% CI, 5.2, 17.2]). As shown in Table 6 and the Kaplan-Meier curves, the benefit of nivolumab, in terms of delaying progression or death, also continued in the longer term, with a proportion of patients remaining alive and progression-free after 24 months of treatment in the nivolumab arm.

Figure 2: Kaplan-Meier plot of progression-free survival in the overall population in CheckMate 141



Data cut-off: 15th October 2019
Abbreviations: IC: investigator's choice.
Source: CheckMate 141 Data on File (15th October 2019)[6]

Table 6: Summary of progression-free survival – overall population

Outcome	Data cut-off: 20th September 2016		Data cut-off: 15th October 2019	
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)
Events, n (%)	[redacted]	[redacted]	214 (89.2)	104 (86.0)
Median PFS, months (95% CI)	[redacted]	[redacted]	2.04 (1.91, 2.14)	2.33 (1.94, 3.06)
6-month PFS rate, % (95% CI)	[redacted]	[redacted]	20.4 (15.4, 26.0)	10.2 (5.2, 17.2)
12-month PFS rate, % (95% CI)	[redacted]	[redacted]	9.5 (6.0, 14.0)	2.6 (0.5, 8.0)
18-month PFS rate, % (95% CI)	[redacted]	[redacted]	8.5 (5.2, 12.8)	NA
24-month PFS rate, % (95% CI)	[redacted]	[redacted]	7.5 (4.5, 11.7)	NA
36-month PFS rate, % (95% CI)	[redacted]	[redacted]	5.3 (2.8, 9.1)	NA

Abbreviations: CI: confidence interval; IC: investigator's choice; NA: not applicable; PFS: progression free survival.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Figure 6.2-1 & Table 6.2-1;[10] Bristol-Myers Squibb Data on File: CheckMate 141 (15th October 2019)

Time to treatment discontinuation

A summary of TTD from the latest data cut of the CheckMate 141 trial (15th October 2019) is presented in Table 7 for the overall population, alongside the original data cut-off presented at CDF entry (20th September 2016). The Kaplan-Meier plot of TTD for the overall population from the latest data cut is presented in in Figure 3. Whilst median TTD is similar between the nivolumab and IC arms ([redacted] months [95% CI, [redacted], [redacted]] for nivolumab versus [redacted] months [95% CI, [redacted], [redacted]] for IC), there is separation of the Kaplan-Meier curves from approximately [redacted]

months. At 24 months, a small proportion ([redacted] [redacted]%]) of patients in the nivolumab arm were still on treatment with nivolumab.

Figure 3: Kaplan-Meier plot of time to treatment discontinuation in the overall population in CheckMate 141

Data cut-off: 15th October 2019
Abbreviations: IC: investigator's choice.
Source: CheckMate 141 Data on File (15th October 2019)[6]

Table 7: Summary of time to treatment discontinuation – overall population

Outcome	Data cut-off: 20th September 2016		Data cut-off: 15th October 2019	
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)
Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median TTD, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; IC: investigator's choice; TTD: time to treatment discontinuation.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Figure 5.1-1,[10] CheckMate 141 Data on File (15th October 2019)[6]

Results from the PD-L1 subgroups (<1% and ≥1%)

As stated earlier, 260 (72.0%) patients in CheckMate 141 had quantifiable PD-L1 expression at baseline, and of these 149 (57.3%) had PD-L1 expression ≥1% and 111 (42.7%) had PD-L1 expression <1%.[5] CheckMate 141 was not powered to detect differences between treatment arms in the different PD-L1 patient subgroups, and so the results of these subgroup analyses should be interpreted with caution. The results by PD-L1 status have, however, been presented below, as requested as part of the CDF review.

The hazard ratios (HRs) from the latest data cut (15th October 2019) for OS with nivolumab versus IC are presented in Table 8. In each of the populations analysed (overall or PD-L1 subgroups), nivolumab was associated with a numerical improvement in OS compared to IC, indicated by a HR of less than one. Additionally, as shown in Figure 4, there is considerable overlap between the 95% confidence intervals (CI) for the HRs for nivolumab versus IC from the PD-L1 <1% and ≥1% subgroups, with the HR in the PD-L1 <1% subgroup located within the 95% CI of the PD-L1 ≥1% subgroup. As such there is not sufficient evidence that there is a statistically significant difference between these subgroups in terms of OS.

The results from each of the PD-L1 subgroups are presented as follows:

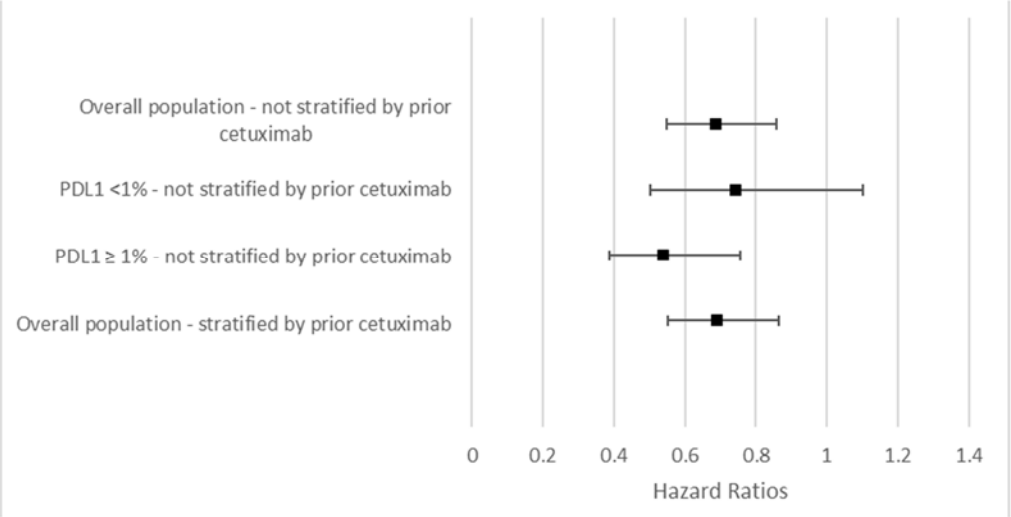
- Figure 5 and Figure 6, for Kaplan-Meier plots of OS in the PD-L1 <1% and PD-L1 ≥1% subgroups, respectively
- Table 9 for a summary of OS rates in the PD-L1 <1% and PD-L1 ≥1% subgroups
- Figure 7 and Figure 8, for Kaplan-Meier plots of PFS in the PD-L1 <1% and PD-L1 ≥1%, respectively
- Table 10 for a summary of PFS rates in the PD-L1 <1% and PD-L1 ≥1% subgroups
- Figure 9 and Figure 10, for Kaplan-Meier plots of TTD in the PD-L1 <1% and PD-L1 ≥1%, respectively
- Table 11 for a summary of TTD rates in the PD-L1 <1% and PD-L1 ≥1% subgroups

Table 8: Hazard ratio for OS with nivolumab versus IC, overall population and PD-L1 subgroups

Population	HR for OS with nivolumab versus IC (95% CI; p-value)	
	Stratified by prior cetuximab[a]	Unstratified[b]
Overall population	0.6901 (0.5514, 0.8637; p=0.001)	0.6858 (0.5483, 0.8579; p<0.001)
PD-L1 <1%	-	0.7429 (0.5015, 1.101; p=0.138)
PD-L1 ≥1%	-	0.5397 (0.3857, 0.7554; p<0.001)

[a] Stratified Cox proportional hazard model. [b] Computed using unstratified Cox proportional hazards model with treatment group as the sole covariate.
Abbreviations: CI: confidence interval; HR: hazard ratio; IC: investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[6]

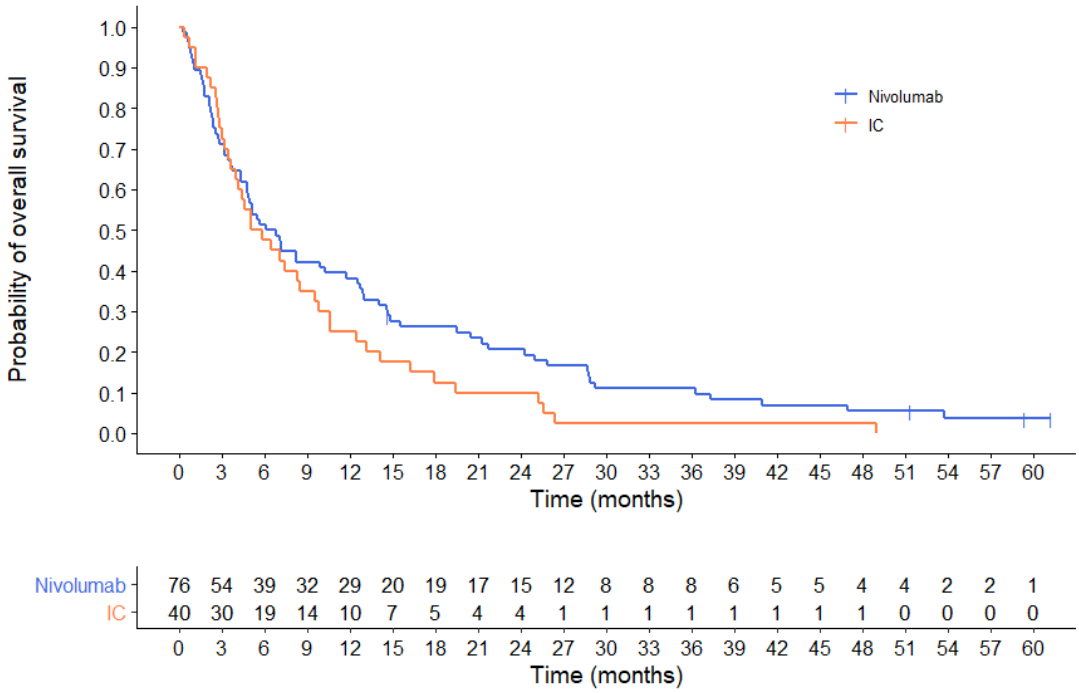
Figure 4: Forest plot of hazard ratios for OS with nivolumab versus IC, overall population and PD-L1 subgroups



Abbreviations: IC: investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[6]

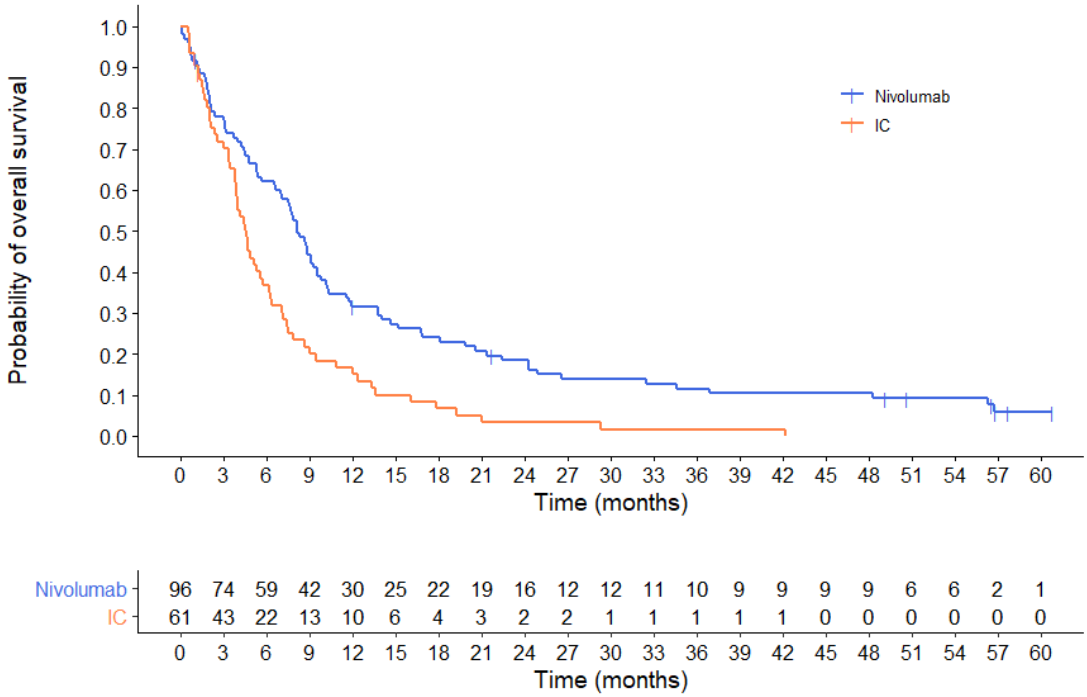
Overall survival

Figure 5: Kaplan-Meier plot of overall survival for patients with the PD-L1 <1% in CheckMate 141



CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[6]

Figure 6: Kaplan-Meier plot of overall survival for patients with the PD-L1 ≥1% in CheckMate 141



CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[6]

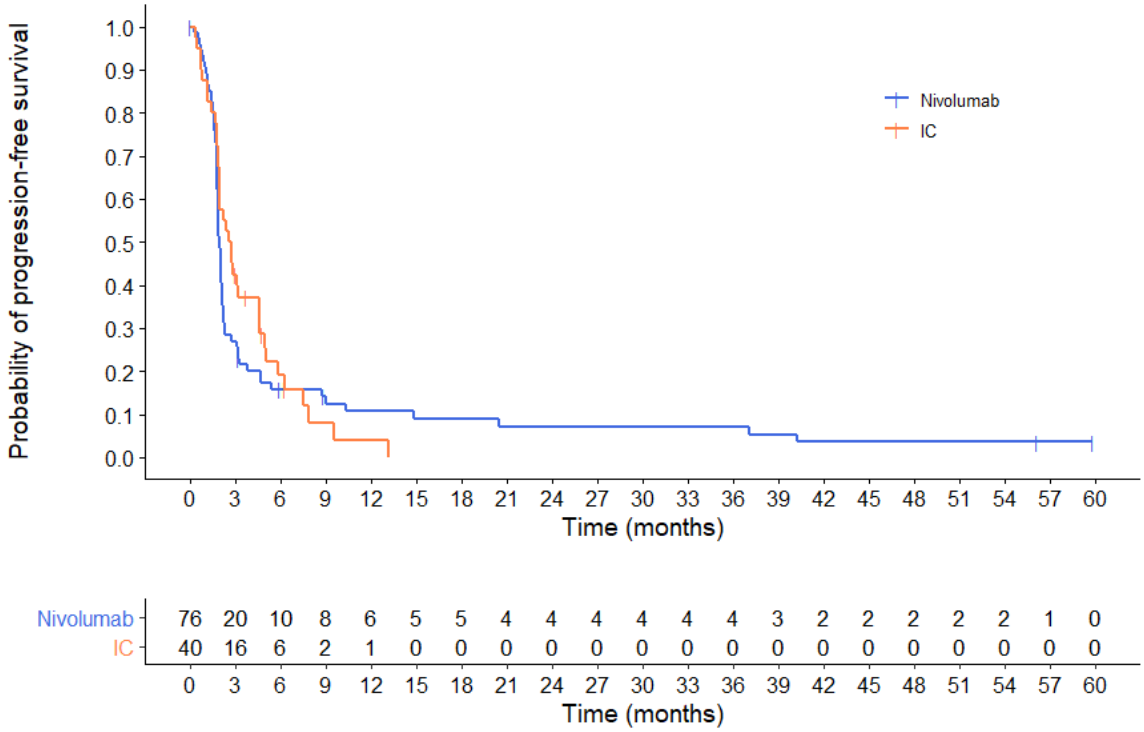
Table 9: Summary of overall survival – PD-L1 subgroups

Subgroup/Outcome	Nivolumab	IC
PD-L1 <1%		
Deaths, n/N (%)	72/76 (94.7)	40/40 (100)
Median OS, months (95% CI)	6.51 (4.37, 11.73)	5.45 (3.68, 8.54)
PD-L1 ≥1%		
Deaths, n/N (%)	87/96 (90.6)	60/61 (98.4)
Median OS, months (95% CI)	8.15 (6.67, 9.53)	4.60 (3.81, 5.78)

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[6]

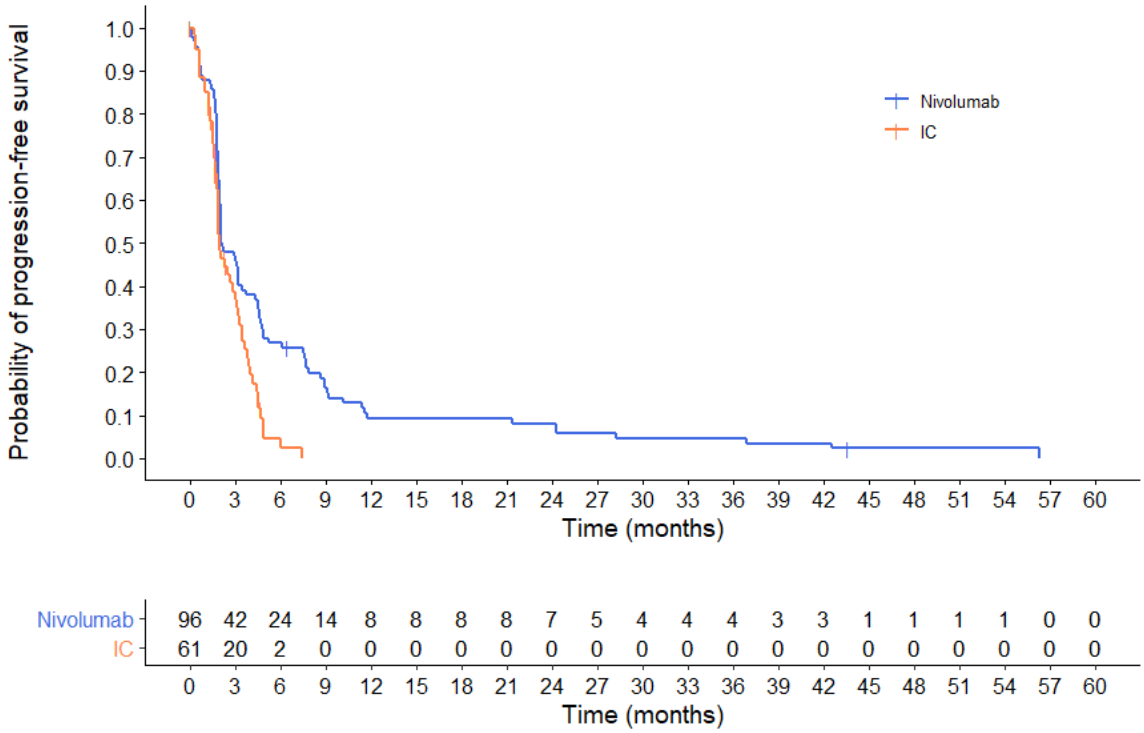
Progression-free survival

Figure 7: Kaplan-Meier plot of progression-free survival for patients with the PD-L1 <1% in CheckMate 141



CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[6]

Figure 8: Kaplan-Meier plot of progression-free survival for patients with the PD-L1 ≥1% in CheckMate 141



CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[6]

Table 10: Summary of progression-free survival – PD-L1 subgroups

Subgroup/Outcome	Nivolumab	IC
PD-L1 <1%		
Events, n/N (%)	69/76 (90.8)	36/40 (90.0)
Median PFS, months (95% CI)	1.95 (1.87, 2.14)	2.68 (1.97, 4.63)
PD-L1 ≥1%		
Events, n/N (%)	88/96 (91.7)	54/61 (88.5)
Median PFS, months (95% CI)	2.14 (1.97, 3.45)	1.97 (1.84, 3.06)

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; IC: investigator's choice; PD-L1: programmed death ligand 1; PFS: progression free survival.
Source: CheckMate 141 Data on File (15th October 2019)[6]

Time to treatment discontinuation

Figure 9: Kaplan-Meier plot of time to treatment discontinuation for patients with the PD-L1 <1% in CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: Bristol-Myers Squibb Data on File: CheckMate 141 (15th October 2019)[6]

Figure 10: Kaplan-Meier plot of time to treatment discontinuation for patients with the PD-L1 ≥1% in CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[6]

Table 11: Summary of time to treatment discontinuation – PD-L1 subgroups

Subgroup/Outcome	Nivolumab	IC
PD-L1 <1%		
Events, n/N (%)	[redacted]	[redacted]
Median TTD, months (95% CI)	[redacted]	[redacted]
PD- L1 ≥1%		
Events, n/N (%)	[redacted]	[redacted]
Median TTD, months (95% CI)	[redacted]	[redacted]

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; IC: investigator's choice; PD-L1: programmed death ligand 1; TTD: time to treatment discontinuation.
Source: CheckMate 141 Data on File (15th October 2019)[6]

Further analyses of EQ-5D

EQ-5D data collected from the 20th September 2016 data cut of the CheckMate 141 trial (across both treatment arms) were analysed to assess how utility might change over time, and specifically how utility might change with respect to how close patients were from death. In summary, for patients who had died in either treatment arm, EQ-5D assessments were grouped by the day of the EQ-5D assessment relative to the date of death. The time from each EQ-5D assessment to death was then used to categorise observations.

Mean estimates of EQ-5D utility (using UK weighting) were then derived for the different time-to-death categories, using all available data collected from the CheckMate 141 trial that were relevant for each time-to-death category (including baseline, follow-up, survival follow-up). Specific censoring rules were used for patients who had not yet died (see Table 12). Data were pooled across treatment arms to derive these estimates due to small numbers of patients in each treatment arm with available data for each time-to-death category. A mixed model approach was used to account for repeated EQ-5D measurements per subject within a given time-to-death category, with time to death included as a fixed effect in the model. Random intercept was used to account for repeated measurements within each subject.

Results of the analyses of utility by time to death are presented in Table 12.

Table 12: Number of patients and observations, and least squares mean estimates from the analysis of utility by time to death

Model	N	Number of observations	Utility value (SE) [95% CI]
Time-to-death (Group 1)[a]			
6+ months	[redacted]	[redacted]	[redacted]
3–6 months	[redacted]	[redacted]	[redacted]
0–3 months	[redacted]	[redacted]	[redacted]
Time-to-death (Group 2)[b]			
57–91 days	[redacted]	[redacted]	[redacted]
29–56 days	[redacted]	[redacted]	[redacted]
0–28 days	[redacted]	[redacted]	[redacted]

[a] EQ-5D assessments from patients who had not died (and were ongoing in the study) and ≥183 days (6+ months) prior to last known alive date were included in the category 6+ months.
[b] EQ-5D assessments from patients who had not died (and were ongoing in the study) were excluded.
Abbreviations: CI: confidence interval; SE: standard error.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016)[10]

Utility values derived from EQ-5D assessments completed 0–3 months from death ([redacted]), 3–6 months from death ([redacted]), and 6+ months from death ([redacted]) (Group 1), show that changes in utility were most apparent during the final three months of life.[10] Changes in utility within the final three months of life were further assessed, with results presented in Table 12 (Group 2). These utility values were then used in the revised base case of the cost-effectiveness model, as described in Section A.8.3.

A.6.2 *SACT data cohort study*

Baseline characteristics

A summary of the baseline characteristics of patients included in the SACT data cohort study versus those from CheckMate 141 is presented in Table 13. It is worth noting that the SACT cohort included 33 (7%) patients with ECOG performance status 2–3, and 65 (13%) patients with missing ECOG status, suggesting that nivolumab has been used in clinical practice for a broader population in terms of performance status than in the CheckMate 141 trial (ECOG performance status 0–1), in line with the European Medicines Agency (EMA) licence in this indication, which does not exclude based on performance status.[7] ECOG performance status in itself is not considered to be a reliable tool for assessing whether patients should receive treatment with nivolumab in practice, given that performance status varies over time and can be classified inconsistently between clinicians.

Table 13: Baseline characteristics of patients in the SACT data cohort study

Characteristic	CheckMate 141; Nivolumab (n=240)	Characteristic	SACT data cohort study
Male, n (%)	197 (82.1)	Male, n (%)	411 (81)
Age, median (years)	59.0	Age, median (years)	62
Age categorisation, n (%)			

<65	172 (71.7)	<40	15 (3)
≥65 & <75	56 (23.3)	40-49	39 (8)
≥75	12 (5.0)	50-59	145 (29)
		60-69	194 (38)
		70-79	104 (21)
		80+	9 (2)
Performance status, n (%)			
0	49 (20.4)	0	122 (24)
1	189 (78.8)	1	286 (57)
≥2	1 (0.4)	2	29 (6)
		3	4 (1)
		4	0 (0)
Missing	1 (0.4)	Missing	65 (13)
PD-L1 score			
<1	73 (30.4)	<1	55 (11)
≥1	88 (36.7)	≥1	52 (10)
Can't be quantified	79 (32.9)	Can't be quantified	189 (37)
		Not recorded	210 (42)

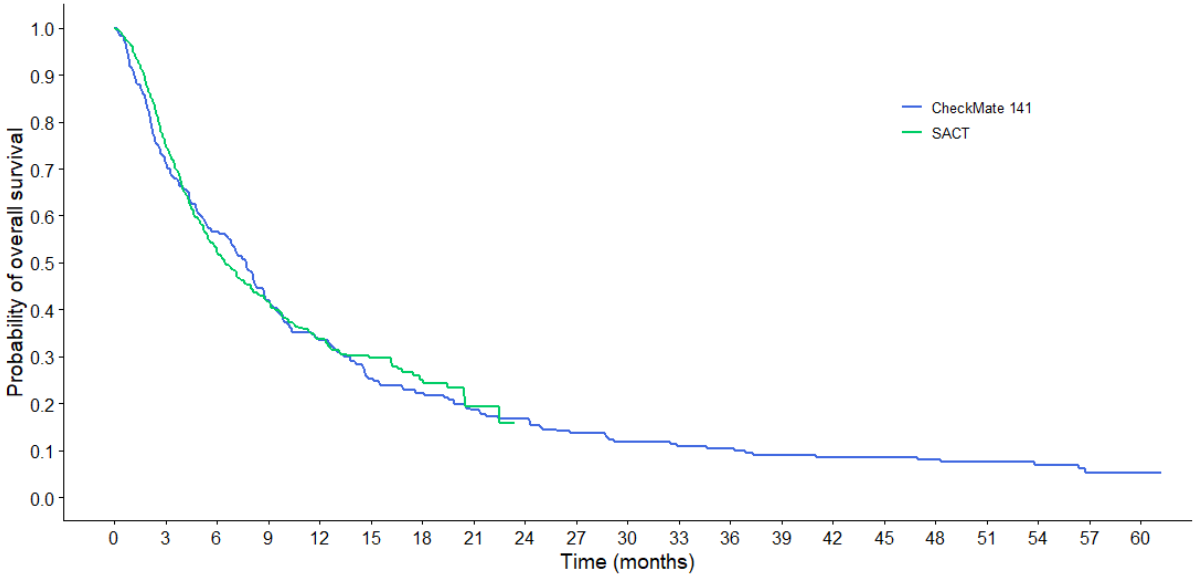
Abbreviations: PD-L1: programmed death ligand 1; SACT: Systemic Anti-Cancer Therapy.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Table 4.2-1-4.2-2[10], Public Health England report[7]

Overall survival

The median OS for all patients in the SACT data cohort was 6.5 months.[7] Survival at 12 months was 34%, compared to 33.4% in the latest data cut of the CheckMate 141 trial (15th October 2019).[6] A comparison of Kaplan-Meier curves for OS from the SACT data cohort and CheckMate 141 is presented in Figure 11.

The striking similarity in OS observed between the SACT data cohort and the CheckMate 141 trial, despite the SACT data cohort including 7% patients with ECOG performance status 2–3, supports the generalisability of the OS data from the CheckMate 141 trial to patients who might receive nivolumab in UK clinical practice.

Figure 11: Kaplan-Meier plot for overall survival from SACT database



CheckMate 141 data cut-off: 15th October 2019
Abbreviations: SACT: Systemic Anti-Cancer Therapy.
Source: CheckMate 141 Data on File (15th October 2019)[6], Public Health England report[7]

Time to treatment discontinuation

The median TTD for all patients in the SACT data cohort was 3.0 months. At 6 and 12 months, 28% and 17% of all patients were still receiving treatment, respectively, compared to [redacted]% and [redacted]% of patients at the latest data cut of the CheckMate 141 trial (15th October 2019). A comparison of Kaplan-Meier curves for TTD from the SACT data cohort and CheckMate 141 is presented in Figure 12.

Figure 12: Kaplan-Meier plot for time to discontinuation from the SACT database

[redacted]

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: SACT: Systemic Anti-Cancer Therapy.
Source: CheckMate 141 Data on File (15th October 2019)[6], Public Health England report[7]

PD-L1 status and SACT

The majority of patients in the SACT cohort had PD-L1 expression that could not be quantified or did not have a score recorded (399 [79%]).[7] This is understood to be partly due to clinicians not testing for PD-L1 expression before providing nivolumab to patients. The low patient numbers with established PD-L1 status limits the usefulness of the SACT data for drawing meaningful conclusions about efficacy in the PD-L1 subgroups in UK clinical practice. Tellingly though, the survival outcomes observed in the subgroup of the SACT cohort for whom PD-L1 was not recorded (n=210) (see Public Health England report; Figure 7; page 26), appears not dissimilar from those with PD-L1 ≥1% (n=52). It would therefore be unreasonable to deny these patients treatment with nivolumab, should treatment only be given to those patients for whom PD-L1 ≥1% can be established in clinical practice.

A.7 Evidence synthesis

Given the availability of direct evidence from the CheckMate 141 trial for the comparison of nivolumab versus investigator's choice (which is used to determine the efficacy of the comparators in the appraisal), no indirect treatment comparison was conducted as part of the original submission.

A.8 Incorporating collected data into the model

Survival analyses were conducted using the latest data from CheckMate 141 (OS, PFS and TTD) in order to extrapolate these outcomes over the modelled lifetime time horizon. The approach to conducting the survival analyses and assessing the appropriateness and plausibility of the resultant curves was the same as that explained in Section 5.3.2 of the original submission and was done in accordance to the guidance issued as part of NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[11]

In addition to standard parametric distributions (exponential, Weibull, loglogistic, lognormal, Gompertz, and generalised gamma) and spline models, piecewise analyses (lognormal and exponential) were also explored for OS in line with the committee's preferred assumptions in TA490.

A.8.1 *Survival inputs: overall population*

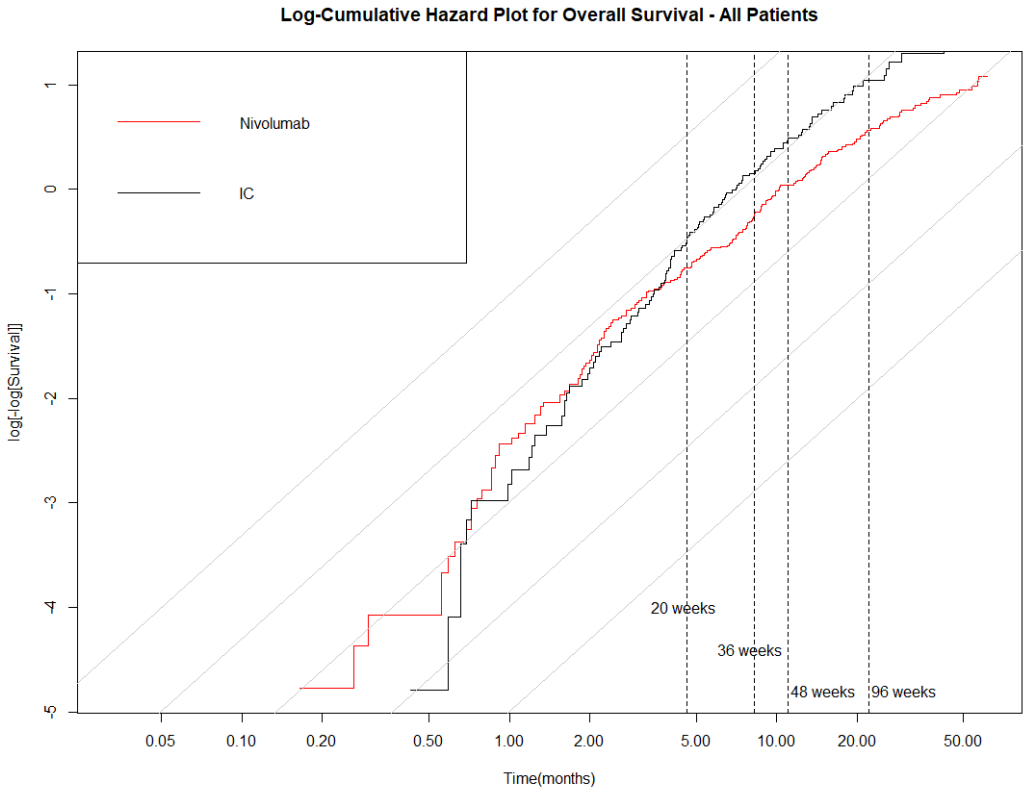
Overall survival

As per the committee's preferred approach in TA490 and the terms of engagement for this review, the piecewise method was used to extrapolate OS from the latest data cut of the CheckMate 141 trial. The distributions that were explored were the exponential distribution, as recommended in Bagust and Beale (2014), and also the lognormal distribution, which represented the committee's preferred extrapolation in TA490.[12] To inform the choice of timepoint to extrapolate from, the log-cumulative hazards plot was inspected (see Figure 13). As per the data cut used in TA490, there is a noticeable change in hazard from Week 20 in both treatment arms. For IC, the hazard appears to be relatively constant over time from Week 20 onwards, whereas for nivolumab there is more of a trend towards a reduction in the hazard over time, which would favour the use of the lognormal distribution. In order to maximise the use of the observed trial data, timepoints later than Week 20 were also explored. This included a much later Week 96 timepoint, in addition to the Week 36 and Week 48 timepoints that were explored in TA490.

Visual inspection of these piecewise extrapolations compared to the observed trial data showed that the exponential distributions (particularly Week 20, 36 and 48) produced a poorer fit than the lognormal distributions (see Figure 14). When looking only at the lognormal distribution, the visual fit was fairly similar across the different timepoints explored, with each providing a reasonable fit to the observed trial data. Only the piecewise models using the lognormal

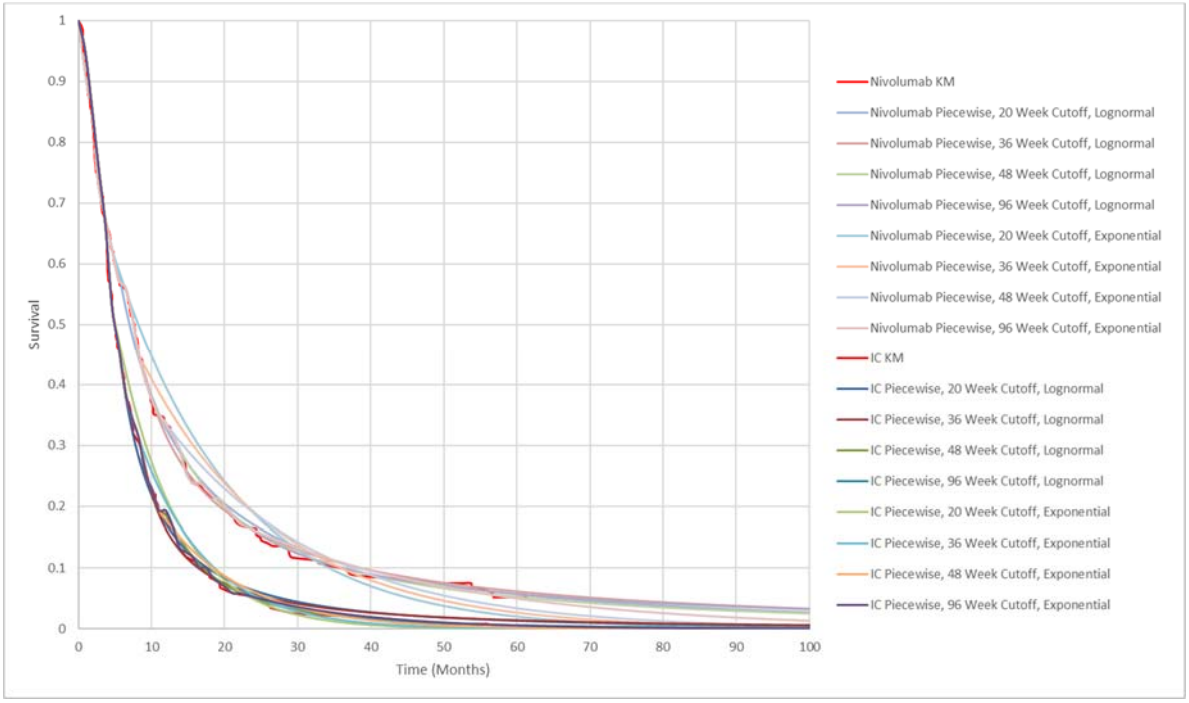
distribution were therefore considered for the revised base case analysis, with preference given to the Week 96 timepoint in order to maximise the use of observed trial data.

Figure 13: Log cumulative hazard plot for overall survival



Abbreviations: IC: investigator's choice.

Figure 14: Long-term OS extrapolation using piecewise models for nivolumab and IC (overall population)

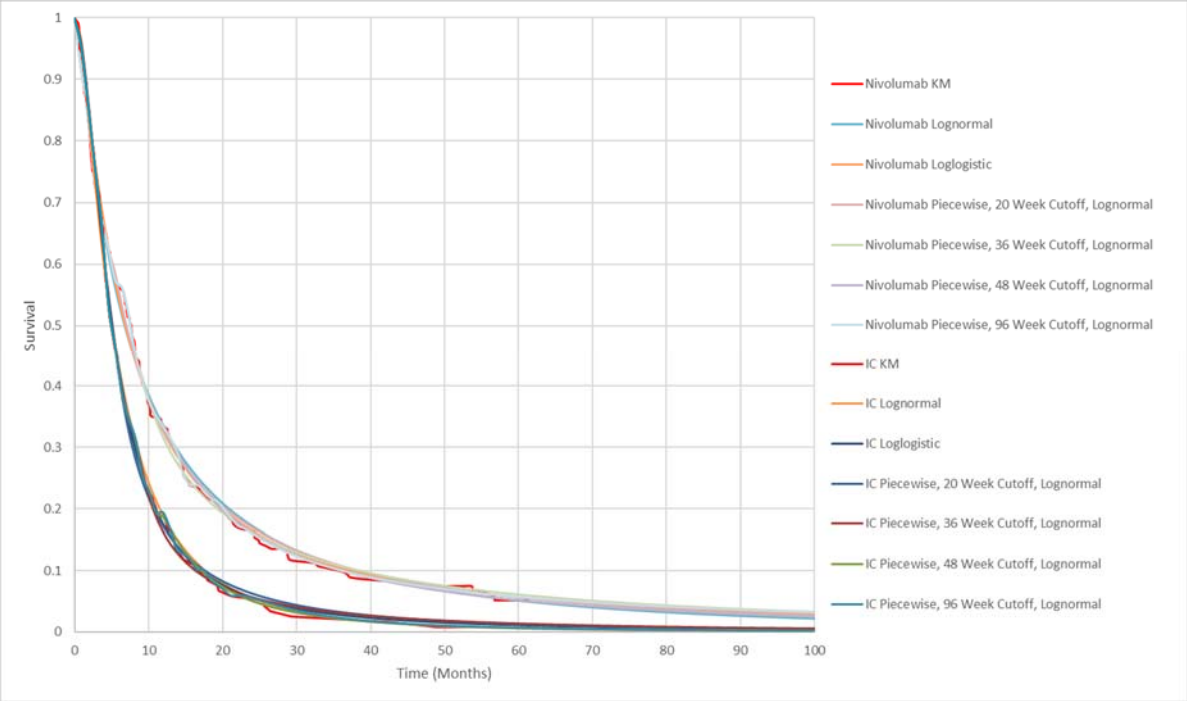


Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; OS: overall survival.

In addition to the piecewise models, fully parametric extrapolations of the observed data were also explored. AIC and BIC values for each fully parametric survival model, and the long-term extrapolations of OS using each model are presented in Appendix B. As per the original submission for TA490, the fully parametric lognormal curve was associated with the best statistical fit to both the nivolumab and IC arms, and provided a reasonable visual fit to the latest observed data from the CheckMate 141 trial. The loglogistic curve, which is also associated with decreasing hazards over time, also provided a reasonable fit to the observed data and was one of the better fitting non-spline curves in terms of AIC and BIC. Long-term extrapolations using the fully parametric lognormal and loglogistic are presented in Figure 15, alongside the lognormal piecewise models.

Based on the above, the fully parametric models are still considered to provide plausible extrapolations of OS with nivolumab and IC and therefore have been explored in scenario analyses in this submission, with the 96-week piecewise used in the base case out of consideration for the committee's preference for the piecewise models in TA490.

Figure 15: Long-term OS extrapolation using fully parametric lognormal and loglogistic models, and piecewise models for nivolumab and IC (overall population)



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

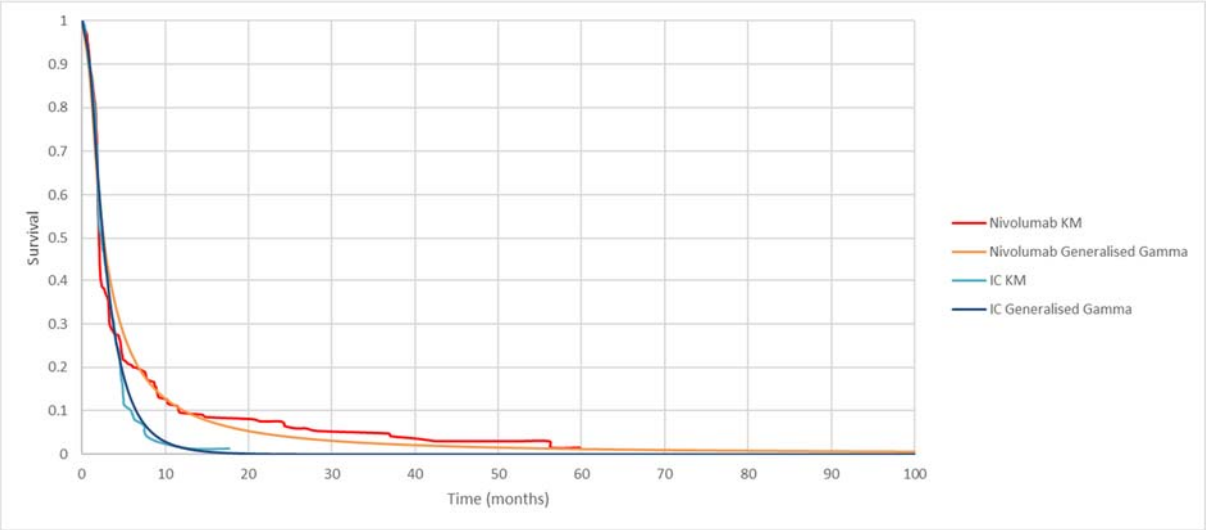
Progression-free survival

A variety of parametric and spline models were explored to extrapolate PFS from the latest data cut of the CheckMate 141 trial. AIC and BIC values for each survival model, and the long-term extrapolations of PFS using each model are presented in Appendix B.

Of those explored, the spline models provided a better statistical fit for nivolumab than the standard parametric models, but the best-fitting curves often produced logical inconsistencies when compared to the preferred extrapolation for OS (with or without the treatment waning effect applied), whereby PFS was higher than OS. Excluding the spline models, the lognormal and loglogistic models provided the best statistical fit for IC but were associated with a poor visual fit to the observed data for nivolumab in the long term. Therefore, as per TA490, the generalised gamma model was selected, providing an improved visual fit for nivolumab compared to the

lognormal and loglogistic models (and best statistical fit of non-spline models for nivolumab) and a reasonable visual fit to the observed data for IC.

Figure 16: Long-term PFS extrapolation of most plausible models for nivolumab and IC (overall population)



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

Time to treatment discontinuation

As for PFS, a variety of parametric and spline models were explored to extrapolate TTD from the latest data cut of the CheckMate 141 trial. AIC and BIC values for each survival model, and the long-term extrapolations of TTD using each model are presented in Appendix B.

[redacted]. For nivolumab, the spline models were associated with the best statistical fit. Of these, the 2 spline normal model provided the best statistical fit and a reasonable visual fit to the observed data. Additionally, compared with mean PFS, mean TTD predicted by the model [redacted]. Extrapolation using the 2 spline normal model was therefore considered to be more plausible for extrapolation of TTD than the generalised gamma model used in TA490.

Figure 17: Long-term TTD extrapolation of most plausible models for nivolumab and IC (overall population)

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

A.8.2 *Survival inputs: patients with PD-L1 <1% and ≥1%*

For patients with PD-L1 <1% and ≥1% receiving nivolumab, the piecewise method was used to extrapolate OS from the latest data cut of the CheckMate 141 trial. The same distributions and timepoints were explored as described in Section A.8.1. As for the overall population, the lognormal piecewise models produced a much better fit compared to piecewise models using the exponential distribution. Piecewise models using a Week 48 timepoint to extrapolate from provided a reasonable fit to the observed data in both PD-L1 <1% and ≥1% subgroups. Week 96 piecewise models were also explored but extrapolations at this later timepoint were based on few patients in each of the subgroups.

As for the overall population, a variety of parametric and spline models were explored to extrapolate PFS for patients with PD-L1 <1% and ≥1% receiving nivolumab, and TTD for patients with PD-L1 ≥1% receiving nivolumab, with consideration given to the statistical and visual fit of the models to the observed data. The extrapolations considered to provide the most plausible estimates of clinical outcomes are summarised in Table 14. AIC and BIC values for each survival model, and the long-term extrapolations of OS, PFS and TTD using each model are presented in Appendix B. Justifications for the choice of selected models are provided in Appendix C.

Table 14: Extrapolations for PD-L1 subgroups

	Selected extrapolations		
	OS	**PFS**	**TTD**
PD-L1 <1%			
Nivolumab	Piecewise lognormal 48-week cut off	Generalised gamma	[redacted]
IC	Kaplan-Meier data	Kaplan-Meier data	[redacted]
PD-L1 ≥1%			
Nivolumab	Piecewise lognormal 48-week cut off	1 spline hazards	1 spline odds
IC	Kaplan-Meier data	Kaplan-Meier data	[redacted]

Abbreviations: IC: investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1; PFS: progression-free survival; TTD: time-to-treatment discontinuation.

A.8.3 *Utility inputs and assumptions*

No further analyses to those conducted in TA490 were undertaken to estimate utility based on progression status. The utility values used for progression-free (PF) and progressed-disease (PD) health states (both treatment-independent and treatment-dependent) are therefore still based on the results of the mixed models in which progression status with and without treatment arm were included as covariates (see FAD Committee Papers 5; BMS additional evidence submitted in response to ACD; Appendix 1).

In order to model changes in utility over time, the economic model includes the option to apply decrements in utility based on time to death. Specifically, utility decrements can be applied for the proportion of patients who are predicted to die within the next three model cycles, with separate decrements applied based on whether patients are one (0–28 days), two (29–56 days) or three (57–84 days) cycles from death. Decrements in utility beyond the three cycles before death are not applied, as analyses of EQ-5D data from CheckMate 141 show that changes in utility were most apparent in the three months prior to death (see Section A.6.1). To estimate the utility decrements, it is assumed that the majority of patients would progress before they died, and would therefore be in the PD state prior to death. It is also assumed that utility prior to death would be the same regardless of treatment arm. The time-to-death utility decrements are therefore based on the difference between the PD utility values used in the model (e.g. for the nivolumab and IC arms, when treatment-dependent utility values are used), and the utility values in each time-to-death category described in Section A.6.1. The utility decrements included in the model are presented in Table 15.

Table 15: Time-to-death utility values and decrements

Utility value	Treatment-dependent		Treatment-independent
	Nivolumab	IC	Both treatment arms
Progressed disease	[redacted]	[redacted]	[redacted]
Time to death			
Three model cycles (57–84 days)[a]	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted][b]	[redacted]
Two model cycles (29–56 days)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]
One model cycle (0–28 days)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]

[a] To reflect that the utility decrement applied in the model was derived from a time-to-death category (57–91 days) longer than a single cycle in the model, the utility decrement was adjusted in the model trace (multiplied by 5/4).
[b] As the time-to-death utility (57–91 days) was greater than the PD utility, no decrement was applied.
Abbreviations: IC: investigator's choice.

A.9 Key model assumptions and inputs

Revised Base Case

In addition to the analyses that have been conducted using the committee's preferred assumptions from TA490 (cost-effectiveness analysis 2), BMS propose a revised base case analysis for this appraisal, using the assumptions and inputs described in Table 16 (cost-effectiveness analysis 3; overall population). These assumptions and inputs are considered to provide the most plausible estimates of clinical outcomes for the overall population, based on the more mature data from CheckMate 141, and also address the concerns raised in TA490 with regards to changes in the utility over time. Scenario analyses have also been conducted to explore alternative extrapolations for OS (using the Week 48 timepoint for the piecewise model, and using the fully parametric lognormal and loglogistic models) and utility assumptions (treatment-specific utility values, with time-to-death utility decrements applied) (Section A.12).

Furthermore, as part of the revised base case:

- As per TA490, the 2-year stopping rule has been applied
- No treatment waning effect after 5 years has been applied for the nivolumab arm
- Treatment-dependent utility values have been used for PF and PD

The use of a stopping rule in routine clinical practice was considered to be acceptable by clinicians consulted as part of original appraisal (FAD Committee Papers 2 and 3; Comments on the ACD) and also NHS England (ACD Committee Papers 5; NHS England statement). In addition, based on the TTD extrapolation used in the base case, [redacted]

Given the availability of long-term (4-year) and more mature data from the CheckMate 141 trial, the need to include a treatment waning assumption is much reduced compared to the original submission for TA490 (2-year). Based on the OS extrapolation used in the base case, less than 6% of patients in the nivolumab arm are predicted to still be alive after 5 years. In addition, at the time of the latest data cut from CheckMate 141, of the thirteen patients in the nivolumab arm who were alive and in follow-up, [redacted],

demonstrating the durability of the survival benefit associated with nivolumab, even after treatment discontinuation.[6] Furthermore, inspection of the log cumulative hazards plot shows that towards the end of the observed follow-up period of CheckMate 141 there is a difference between treatment arms in the change in hazard over time (see Figure 13), with a reduction in the hazard over time being observed in the nivolumab arm, compared to a relatively constant hazard in the IC arm. Should this trend continue beyond the 4-year follow-up period, it would not be appropriate to assume that the hazard in the nivolumab arm would be the same as the IC arm, as is done to model the treatment waning effect. Given the considerations outlined above, it is considered more plausible to predict long-term survival with nivolumab without applying the treatment waning effect at 5 years.

The treatment-specific utility values for PF and PD have been used in the revised base case analysis to reflect the benefits in health-related quality of life that are provided with nivolumab, as was recognised by clinical experts consulted as part of TA490 (ACD; 4.16 and 4.17).[13] These utility values were derived from EQ-5D data collected during the CheckMate 141 trial and demonstrate the improved utility post-progression for patients who were randomised to receive nivolumab versus IC. Furthermore, the mixed model that included progression status and treatment arm (used to derive treatment-specific utility values) was associated with a better statistical fit than the model including progression status alone (treatment-independent utility values) (see FAD Committee Papers 5; BMS additional evidence submitted in response to ACD; Appendix 1). Given the differences between the nivolumab and IC arms in the number of EQ-5D observations, particularly post-progression (n=[redacted] for nivolumab and n=[redacted] for IC), the treatment-independent utility values are mainly driven by the experiences of patients in the nivolumab treatment arm. As well as failing to account for potential differences between treatment arms, these values are therefore also not considered to be an accurate reflection of the utility of patients who receive IC.

Scenario analyses have, however, been conducted in which the treatment waning assumption is applied (at 5, 7 and 10 years), the stopping rule is removed, and in which treatment-independent utility values are used for PF and PD (see Section A.12). For the reasons discussed above, it was considered more plausible to predict long-term survival with nivolumab without applying the treatment waning effect at 5 years, given the durability of survival benefit for patients in the nivolumab arm of the CheckMate 141 trial who were alive in follow-up, and the trends in the hazard up to 4 years. Therefore, of the scenarios that do explore a treatment waning assumption, those using later timepoints from which to apply the treatment waning effect are considered to be more plausible than the scenario using the 5-year timepoint (the committee-preferred assumption in TA490). To reflect the possibility that some patients treated with nivolumab may maintain improvements in survival beyond the timepoints used in the treatment waning scenarios, analyses have also been conducted in which the treatment waning effect (i.e. setting the probability of death to be the same as IC) is only applied to a proportion of patients, with the remaining patients having survival modelled based on the chosen extrapolation. In these “partial” treatment waning scenarios, the proportion of patients for whom the treatment waning effect is not applied has been based on the proportion of patients in the CheckMate 141 trial who achieved a best overall response of complete response, partial response or stable disease ([redacted]%) (i.e. it is assumed that the patients who would maintain survival benefits are those who would have either achieved a response or at least have had stable disease).[10]

In the scenario in which treatment-independent utility values have been used, decrements in utility based on time to death have been applied (as described in Section A.8.3).

As part of the revised base case, the ERG’s amendments to the original model: adding the cost and disutility for pneumonitis and using treatment-independent proportions for subsequent treatments [[redacted]] – based on the average percentage of patients receiving subsequent systemic anti-cancer therapy in the nivolumab and IC arms from the 20th September 2016 database lock of CheckMate 141, have all been included.

Table 16: Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
OS, PFS and TTD data source [5.3.2 (page 101)]	CheckMate 141 (Data cut-off: 20th September 2016)	CheckMate 141 (Data cut-off: 15th October 2019)	Further follow-up data from the pivotal trial (CheckMate 141) has been incorporated into the model.
OS extrapolation [FAD Committee Papers 8; appendix with 2-year stopping rule]	Nivolumab and IC: piecewise with lognormal (20, 36 and 48 week cut-off points)	Nivolumab and IC: piecewise with lognormal (96 week cut-off point)	The committee-preferred assumption of a piecewise approach has been used in the base case. The lognormal distribution provided a better visual fit to the observed trial data compared to the exponential distribution when considering the piecewise models that were preferred by the committee in TA490. The 96 week cut-off point was selected to maximise the use of the observed trial data. Scenarios have also been presented using fully parametric models, as these are still considered to provide plausible extrapolations.
Long-term treatment waning effect [ACD Committee Papers 10; additional evidence provided by the company]	Treatment waning at 5 years included	Treatment waning at 5 years excluded	Given the availability of long-term (4-year) and more mature data from the CheckMate 141 trial, the need to include a treatment waning assumption is much reduced compared to the original submission for TA490 (2-year). Inspection of the log cumulative hazards plot shows that towards the end of the observed follow-up period of CheckMate 141 there is a difference between treatment arms in the change in hazard over time, and should these trends continue, the assumptions for modelling the treatment waning effect after 5 years would not be valid. Additionally, durable survival benefit was observed for patients in the nivolumab arm of the CheckMate 141 trial who were alive in follow-up. Scenarios have been presented in which the treatment waning effect is applied after 5, 7 and 10 years. Scenarios in which treatment waning is only applied to a proportion of patients ("partial" treatment waning), based on whether patients had a best overall response of CR/PR/SD, have also been conducted to reflect the possibility that some patients treated with nivolumab

			may maintain improvements in survival beyond the timepoints used for treatment waning.
PFS extrapolation [5.6.1 (page 143)]	Nivolumab and IC: generalised gamma	Nivolumab and IC: generalised gamma	As per TA490, the generalised gamma model was selected for extrapolation of PFS, providing good visual fit for nivolumab (and best statistical fit of non-spline models for nivolumab) and a reasonable visual fit for IC. The spline models provided a better statistical fit for nivolumab than the standard parametric models, but the best fitting curves often produced logical inconsistencies with the preferred extrapolation for OS (i.e. PFS was predicted to be higher than OS). Excluding the spline models, the lognormal and loglogistic models provided the best statistical fit for IC but were associated with a poor visual fit to the observed data for nivolumab in the long term.
TTD extrapolation [ACD Committee Papers 10; additional evidence provided by the company]	Nivolumab and IC: generalised gamma	Nivolumab: 2 spline normal IC: [redacted]	For nivolumab, the 2 spline normal model provided the best statistical fit and a reasonable visual fit to the observed data, and was thus considered to be more plausible for extrapolation of TTD than the generalised gamma model used in TA490. The 2 spline model also predicted a reasonable estimate of mean TTD when compared to PFS (i.e. mean TTD and mean PFS were similar) [redacted]
Utility values [FAD Committee Papers 5; BMS additional evidence submitted in response to ACD; Appendix 1]	**Treatment-specific** PF nivolumab: [redacted] PD nivolumab: [redacted] PF IC: [redacted] PD IC: [redacted] **Treatment independent** PF: [redacted] PD: [redacted]	**Treatment-specific** PF nivolumab: [redacted] PD nivolumab: [redacted] PF IC: [redacted] PD IC: [redacted] With time-to-death utility decrements applied	Treatment-specific utility values for PF and PD have been used to reflect the benefits in health-related quality of life that may be expected with nivolumab, as was recognised by clinical experts consulted as part of TA490 (ACD; 4.16 and 4.17). These utility values were derived from EQ-5D data collected during the CheckMate 141 trial, with the mixed model used to derive the treatment-specific utility values being associated with a better statistical fit than the model including progression status alone (treatment-independent utility values). Time-to-death utility decrements have been applied in order to address concerns raised in TA490 and model changes in utility

			over time. These utility decrements are based on utility values derived from EQ-5D data collected during the CheckMate 141 trial. A scenario has been presented in which treatment-independent utility values have been used.
Stopping rule [FAD Committee Papers 8; appendix with 2-year stopping rule]	2-year stopping rule included	No change	The use of a stopping rule in routine clinical practice was considered to be acceptable by clinicians consulted as part of original appraisal (FAD Committee Papers 2 and 3; Comments on the ACD) and also NHS England (ACD Committee Papers 5; NHS England statement). In addition, based on the TTD extrapolation used in the base case, [redacted]
ERG's amendments to the company's model [ACD Committee Papers 7; ERG report]	Adding the cost and disutility for pneumonitis and using treatment-independent proportions for subsequent treatment	No change	-

Abbreviations: ACD: Appraisal Consultation Document; CR: complete response; ERG: Evidence Review Group; FAD: Final Appraisal Determination; IC: investigator's choice; OS: overall survival; PD: progressed disease; PF: progression free; PFS: progression-free survival; PR: partial response; SD: stable disease; TTD; time to treatment discontinuation.

A.10 Cost-effectiveness results (deterministic)

A.10.1 *Overall population*

The key cost-effectiveness results considered by the committee to demonstrate plausible potential for cost-effectiveness at entry to the CDF have been replicated in Table 17 (Cost-effectiveness analysis 1) and the results of the analysis that incorporated the data collected during the CDF data collection period, with all model inputs and parameters (aside from a change in dosing schedule from weight-based to flat) unchanged from the original cost-effectiveness analysis, are presented in Table 18 (Cost-effectiveness analysis 2). All analyses include a PAS discount of [redacted]% to the list price of nivolumab.

A variety of assumptions were explored in these analyses, as per the original submission:

- Using the piecewise model using the lognormal distribution to model overall survival – extrapolated from 20, 36 and 48 weeks
- Using both treatment-dependent and treatment-independent utility values

The cost-effectiveness analyses described above have also been replicated using the weight-based dose for nivolumab and full details of the results are presented in Appendix D.

The results for the revised base case are presented in Table 19 (Cost-effectiveness analysis 3) for the overall population, incorporating the assumptions as described in Section A.9.

Table 17: Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (with PAS) – overall population, flat dose

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)
Piecewise lognormal cut-off point:	**20 weeks**			**36 weeks**			**48 weeks**		
Treatment-specific utility									
Docetaxel	[redacted]	[redacted]	£45,874	[redacted]	[redacted]	£41,304	[redacted]	[redacted]	£53,634
Paclitaxel	[redacted]	[redacted]	£42,252	[redacted]	[redacted]	£38,065	[redacted]	[redacted]	£49,363
Methotrexate	[redacted]	[redacted]	£43,215	[redacted]	[redacted]	£38,925	[redacted]	[redacted]	£50,498
Treatment-independent utility									
Docetaxel	[redacted]	[redacted]	£58,448	[redacted]	[redacted]	£52,528	[redacted]	[redacted]	£67,555
Paclitaxel	[redacted]	[redacted]	£53,833	[redacted]	[redacted]	£48,409	[redacted]	[redacted]	£62,175
Methotrexate	[redacted]	[redacted]	£55,059	[redacted]	[redacted]	£49,503	[redacted]	[redacted]	£63,604

Abbreviations: CDF: Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; PAS: Patient Access Scheme; QALYs, quality-adjusted life years.

Table 18: Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence (with PAS) – overall population, flat dose

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)
Piecewise lognormal cut-off point:	**20 weeks**			**36 weeks**			**48 weeks**		
Treatment-specific utility									
Docetaxel	[redacted]	[redacted]	£43,959	[redacted]	[redacted]	£41,906	[redacted]	[redacted]	£45,793
Paclitaxel	[redacted]	[redacted]	£40,644	[redacted]	[redacted]	£38,757	[redacted]	[redacted]	£42,333
Methotrexate	[redacted]	[redacted]	£41,527	[redacted]	[redacted]	£39,596	[redacted]	[redacted]	£43,255
Treatment-independent utility									
Docetaxel	[redacted]	[redacted]	£53,510	[redacted]	[redacted]	£50,728	[redacted]	[redacted]	£55,051
Paclitaxel	[redacted]	[redacted]	£49,474	[redacted]	[redacted]	£46,916	[redacted]	[redacted]	£50,892
Methotrexate	[redacted]	[redacted]	£50,550	[redacted]	[redacted]	£47,932	[redacted]	[redacted]	£52,000

Abbreviations: CDF: Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; PAS: Patient Access Scheme; QALYs, quality-adjusted life years.

Revised base case

Table 19: Cost-effectiveness analysis 3: New company base-case (with PAS) – overall population, flat dose

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	1.31	[redacted]				
Docetaxel	£10,569	0.67	0.35	[redacted]	0.65	[redacted]	£37,236
Paclitaxel	£12,000	0.67	0.35	[redacted]	0.65	[redacted]	£34,186
Methotrexate	£11,609	0.67	0.35	[redacted]	0.65	[redacted]	£35,019

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

A.10.2 *Patients with PD-L1 <1% and ≥1%*

As discussed in Section A.6.1, the clinical effectiveness results by PD-L1 status should be interpreted with caution, as CheckMate 141 was not powered to detect a difference between treatment arms in these subgroups. As shown in Figure 4, the overlap between the 95% CI of HRs for nivolumab versus IC in each of the PD-L1 subgroups demonstrates that there is no statistically significant difference between the subgroups in the treatment effect on OS. The HRs themselves do indicate that treatment with nivolumab is of benefit versus standard of care, regardless of PD-L1 status.

BMS believe that the evidence is such that the overall population should be considered as the patient population within the CDF review. The implications of providing a recommendation based on PD-L1 status would mean patients who would benefit from treatment are denied access (either due to a lack of or inconclusive tests [as demonstrated in the SACT data, where 79% of patients had missing or inconclusive PD-L1 data], or due to the occurrence of false negatives). However, cost-effectiveness results by PD-L1 status have been presented here, for completeness and to adhere to the terms of engagement.

A summary of cost-effectiveness results (versus docetaxel only) for the PD-L1 subgroups (<1% and ≥1%) is presented in Table 20. The results for the revised base case (Cost-effectiveness analysis 3) incorporate the inputs and assumptions as described in Section A.9, with the exception of OS, PFS and TTD extrapolations, which were based on those described in Section A.8.2. Full cost-effectiveness results are presented in Appendix D with the PAS applied for nivolumab.

Table 20: Summary of cost-effectiveness analyses and revised base case (with PAS) versus docetaxel only – PD-L1 subgroups, flat dose

Analysis		**ICER (£/QALY gained) versus docetaxel**	
Utility values		**Treatment-specific**	**Treatment-independent**
PD-L1 <1%			
Cost-effectiveness analysis 1, flat dose			
Piecewise lognormal cut-off point	20 weeks	£39,218	£53,242
	36 weeks[a]	-	-
	48 weeks	£65,154	£102,195
Cost-effectiveness analysis 2, flat dose			
Piecewise lognormal cut-off point	20 weeks	£42,558	£54,341
	36 weeks[a]	-	-
	48 weeks	£47,982	£61,729
Cost-effectiveness analysis 3, flat dose		£46,309	-
PD-L1 ≥1%			
Cost-effectiveness analysis 1, flat dose			
Piecewise lognormal cut-off point	20 weeks	£43,647	£51,809
	36 weeks	£35,882	£41,020
	48 weeks	£41,581	£47,714
Cost-effectiveness analysis 2, flat dose			
Piecewise lognormal cut-off point	20 weeks	£42,945	£49,710
	36 weeks	£42,061	£48,051
	48 weeks	£44,045	£50,253

Analysis	ICER (£/QALY gained) versus docetaxel	
Utility values	**Treatment-specific**	**Treatment-independent**
Cost-effectiveness analysis 3, flat dose	£36,163	-

[a] As noted in FAD Committee Papers 8; appendix, with 2-year stopping rule, the extrapolation of OS using the piecewise model with the 36 week cut-off point was not considered plausible, particularly for the PD-L1 <1% subgroup. This cut-off point creates a kink in the shape of the survival curve for IC which causes the IC curve to cross the nivolumab curve and produce a plateau after 3 years. The resulting survival curve is therefore wholly clinically implausible given the known prognosis for patients with R/M SCCHN after platinum therapy. ICERs have therefore not been presented from the PD-L1 <1% subgroup using the 36 week cut-off point.

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: Patient Access Scheme; PD-L1: programmed death ligand 1; QALYs, quality-adjusted life years; R/M SCCHN: recurrent/metastatic squamous cell carcinoma of the head and neck.

A.11 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted using a Monte-Carlo simulation with 1,000 iterations. In each iteration, the model inputs were randomly drawn from the specified distributions, as summarised in Appendix E. Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a particular value, it was varied by ±15%.

The results of the PSA (based on the overall population, with the PAS applied) are provided in Table 21. The probabilistic results (that take into account the combined uncertainty across model parameters) are similar to those estimated in the deterministic base case analysis, confirming the robustness of the base case analysis.

A scatter plot of incremental costs and QALYs for nivolumab (with PAS) versus docetaxel is presented in Figure 18. Scatter plots of incremental costs and QALYs for the comparisons of nivolumab versus paclitaxel and methotrexate are presented in Appendix E. Assuming a willingness-to-pay threshold of £50,000 per QALY gained, the probability of nivolumab being the most cost-effective treatment option was 75.6% (with the PAS applied). The cost-effectiveness acceptability curves for nivolumab (with PAS) versus all comparators are presented in Figure 19.

Table 21: Revised base case results (average probabilistic) (with PAS) – overall population, flat dose

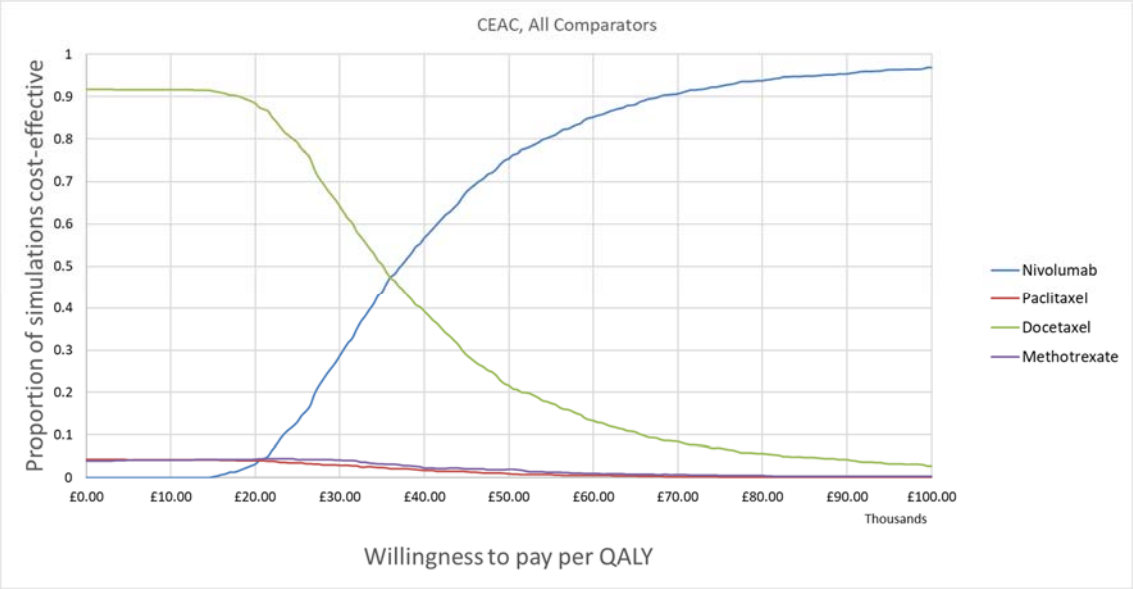
Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,574	0.36	[redacted]	[redacted]	£36,255
Paclitaxel	£11,983	0.36	[redacted]	[redacted]	£33,340
Methotrexate	£11,638	0.36	[redacted]	[redacted]	£34,059

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

Figure 18: Cost-effectiveness plane for nivolumab (with PAS) versus docetaxel – overall population, flat dose

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 19: Cost-effectiveness acceptability curve for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate – overall population, flat dose



Abbreviations: CEAC: cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

A.12 Key sensitivity and scenario analyses

Deterministic Sensitivity Analysis

Deterministic sensitivity analysis (DSA) was conducted by varying all parameters for which there were single input values in the model. Whenever available, values were varied using the standard error obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a particular value, it was varied by ±20%.

A tornado diagram showing the top ten drivers of cost-effectiveness in the comparison of nivolumab versus docetaxel, when nivolumab is provided with the PAS discount, is presented in Figure 20. Tornado diagrams for the comparisons of nivolumab versus paclitaxel and methotrexate are presented in Appendix E. For the comparison of nivolumab versus docetaxel, it

can be seen that the most influential parameters included in the DSA were variables relating to the treatment frequency of nivolumab and health-state utility values. These parameters were the also the most influential in the original analyses in TA490, demonstrating the stability of the results. Parameters relating the survival inputs were not however included in the DSA.

Figure 20: Tornado diagram of the ten most influential parameters: nivolumab (with PAS) versus docetaxel – overall population, flat dose

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

Scenario Analyses

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis and the results of these scenarios (where nivolumab is provided with the PAS discount) are presented in Table 22. Results have only been presented for comparisons of nivolumab versus docetaxel, since these comparisons are associated with the highest ICERs and therefore represent the most conservative comparison from the perspective of cost-effectiveness of nivolumab.

As shown in Table 22, nivolumab (with PAS) is associated with an ICER of less than £50,000 per QALY gained versus docetaxel in each of the key scenarios, including scenarios using treatment-independent utilities for PF and PD, and those applying a ("partial" or full) treatment waning effect at different timepoints. The scenario with the greatest impact on the base case ICER was the exclusion of the 2-year stopping rule. Based on the TTD extrapolation used in the base case, and a 2-year stopping rule has been shown to be clinically plausible during the CDF data collection period. Therefore, this scenario is unlikely to represent clinical practice.

In the scenarios exploring alternative OS assumptions (without treatment waning), the ICERs versus docetaxel were similar to the base case analysis (all within £4,000), and all were less than £50,000 per QALY gained. The results of these scenarios – which use the latest data from the CheckMate 141 trial and explore both piecewise and fully parametric extrapolation approaches – are considered to address the main area of uncertainty in the original TA490 appraisal (i.e. uncertainty in long-term OS benefits).

Table 22: Key scenario analyses (with PAS) versus docetaxel – overall population, flat dose

Scenario	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on base-case ICER
Base case		£37,236	-
Alternative OS assumption	Piecewise lognormal 48-week cut-off for OS extrapolation	£40,167	+£2,931
Alternative OS assumption	Fully parametric lognormal	£41,158	+£3,922
Alternative OS assumption	Fully parametric loglogistic	£38,896	+£1,660
Treatment-dependent utility values	• Treatment-dependent utility values • No time-to-death utility decrements	£35,340	-£1,896
Treatment-independent utilities	• Treatment-independent utility values • Time-to-death utility decrements	£41,418	+£4,182
Treatment-independent utilities	• Treatment-independent utility values • No time-to-death utility decrements	£41,537	+£4,301
No stopping rule	2-year stopping rule is not applied	£49,018	+£11,782
Treatment waning (5 years)	Treatment waning applied from 5 years	£45,014	+£7,778
Treatment waning (7 years)	Treatment waning applied from 7 years	£41,639	+£4,403
Treatment waning (10 years)	Treatment waning applied from 10 years	£39,214	+£1,978
"Partial" treatment waning (5 years)	Treatment waning applied from 5 years for [redacted]% of patients only	£41,821	+£4,585
"Partial" treatment waning (7 years)	Treatment waning applied from 7 years for [redacted]% of patients only	£39,921	+£2,685
"Partial" treatment waning (10 years)	Treatment waning applied from 10 years for [redacted]% of patients only	£38,472	+£1,237

Abbreviations: ICER: incremental cost effectiveness ratio; OS: overall survival.

A.13 End-of-life criteria

Nivolumab was considered to have met NICE's end-of-life criteria in the original appraisal.

A.14 Key issues and conclusions based on the data collected during the CDF review period

The mature data now available from CheckMate 141 provides compelling evidence of the long-term benefit of nivolumab versus IC as a treatment for adults with R/M SCCHN after platinum-based therapy. The survival rates in the nivolumab arm of the CheckMate 141 trial remain consistently higher than IC at 12, 24, 36 and 48 months of follow-up and after 4 years, 8.0% of patients in the nivolumab arm were still alive, four times that on treatment with IC.[6] Improvements in median OS with nivolumab versus IC were also observed in both PD-L1 ≥1% and PD-L1 <1% subgroups and there is not sufficient evidence from the trial to suggest that the numerical improvement in OS with nivolumab versus IC observed is statistically significantly different between the two subgroups.[6]

Data collected from the SACT cohort study demonstrates the generalisability of results from the CheckMate 141 trial to patients receiving nivolumab in UK clinical practice, with a similar proportion of patients reported to be alive at 12 months in both the SACT data cohort study and the CheckMate 141 trial. Limited information on PD-L1 status was collected as part of the SACT data cohort study. However, OS for patients with PD-L1 ≥1% in the SACT data cohort (n=52) and those who did not have PD-L1 expression recorded (n=210) was similar, indicating that nivolumab is efficacious for patients regardless of whether PD-L1 testing is performed.[7]

Evidence demonstrating the clinical- and cost-effectiveness of nivolumab in each of the PD-L1 subgroups has been provided as part of this appraisal, in line with the terms of engagement document. However, the results from the overall population demonstrates that nivolumab would be a cost-effective treatment option for all patients with R/M SCCHN after platinum-based therapy.

In the overall population, the cost-effectiveness results for nivolumab versus each of the comparators has improved on inclusion of the more mature clinical data from the CheckMate 141 trial (see Table 17 and Table 18). In the revised base case analysis, which also accounts for changes in utility over time, nivolumab has been shown to be a cost-effective use of NHS resources in the overall population, being associated with an ICER less than £50,000 per QALY gained versus docetaxel when the stopping rule is applied. The results of the base case analysis were robust to underlying parameter uncertainty, as shown in the PSA, and ICERs less than £50,000 per QALY gained versus docetaxel were also produced when more pessimistic assumptions regarding the long-term effectiveness (treatment waning scenarios) and health-related quality of life benefits (treatment-independent utilities scenario) of nivolumab were applied. The scenarios exploring alternative OS extrapolations without treatment waning produced similar ICERs to the base case analysis (which used the piecewise modelling approach preferred by the committee), and demonstrate that the cost-effectiveness results are robust to different assumptions regarding long-term OS, which was the main area of uncertainty in the original TA490 appraisal.

The new data from CheckMate 141 validates the improvements in long-term survival and health-related quality of life that nivolumab provides compared to IC. These updated analyses demonstrate that nivolumab is a cost-effective treatment option for patients with R/M SCCHN after platinum-based therapy and should be available to patients in England through routine commissioning.

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Appendices

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (CDF Review of TA490) [ID1585]

Clarification questions

March 2020

File name	Version	Contains confidential information	Date
ID1585 nivolumab_company response to clarification letter-_Redacted	1.0	Yes	19/03/20

Section A: Clarification on effectiveness data

A1. Priority question. The company has performed all clinical effectiveness analyses based on data from the whole CheckMate 141 trial population regardless of investigator choice (IC). However, the main comparator, as stipulated in the Terms of Engagement, is docetaxel: "Docetaxel is the comparator of interest in the CDF review".

a. Please provide all analyses based on only the subgroup of patients eligible for docetaxel (who would have been chosen to receive docetaxel according to IC), i.e. those patients who were randomised to docetaxel vs. those who would have received docetaxel according to IC, but who were randomised to nivolumab. These analyses should include overall survival (OS), progression free survival (PFS), and time to treatment discontinuation (TTD). All usual summary measures should be reported including hazard ratios.

b. Please also complete these analyses for each of the PD-L1 subgroups.

In the timeframe given for the company response it would not have been possible to complete the requests relating to the comparisons using data from patients intended for docetaxel only in the CheckMate 141 trial.

Such a comparison between nivolumab and IC for patients intended to receive docetaxel in the CheckMate 141 trial was performed in response to the clarification questions for the original submission (see TA490 ACD; Committee Papers; Section 4; pages 303–331). The results of the cost-effectiveness analysis from this comparison were very similar to those presented in the original company submission base case which utilised data from the IC arm for each of the comparators (see TA490 ACD; Committee Papers; Section 3; page 209). The incremental LYs gained versus docetaxel was 0.68 in the original base case (ICER versus docetaxel of £34,902 per QALY gained) and 0.73 (ICER versus docetaxel of £34,286 per QALY gained) in the scenario analysis using data from patients intended to receive docetaxel only. This demonstrated that the comparisons using the docetaxel-matched subgroup that have been requested would have minimal impact on the cost-effectiveness results.

Regardless of the feasibility of completing these analyses in the allowed timeframe, the approach taken in the company evidence submission is considered to be most appropriate for the purposes of the Cancer Drugs Fund (CDF) review:

- CheckMate 141 was designed to be powered to detect differences between treatment arms (nivolumab versus IC of therapy) and was therefore not powered to detect differences between nivolumab and the individual therapies comprising IC. A comparison versus docetaxel alone is therefore less robust than that using the total IC population, due to the resulting small sample sizes, and a focus on this subgroup analysis for decision making should be discouraged, particularly when this subgroup does not fully capture the intended population for nivolumab (i.e. patients who might otherwise be intended for methotrexate or other single-agent therapies). Conducting the analysis in the overall population results in sample sizes of only 88 nivolumab patients and 54 docetaxel

patients (intended for docetaxel) compared to 240 and 121 patients in the nivolumab and IC arms (overall population), respectively. Analyses of efficacy by PD-L1 status would also be limited by the further reduction in sample sizes if looking only at patients who were intended to receive docetaxel.

- The choice of intended IC therapy was made prior to randomisation at the investigator's discretion. The analysis of outcomes by individual therapies in the IC arm therefore breaks randomisation and are at risk of selection bias.
- As detailed in the Final Appraisal Determination (FAD), the committee concluded that the company's model structure using estimated OS, PFS and TTD based on data from the IC arm for docetaxel, methotrexate and paclitaxel was appropriate for decision making.
- All cost-effectiveness results presented in the Final Appraisal Determination (FAD) of TA490 were based on analyses using efficacy data from the investigator's choice (IC) arm of the CheckMate 141 trial. As the Terms of Engagement stipulates that NICE expects the committee's preferred assumptions to remain unchanged at the CDF review, the same approach that was used in TA490 was taken in the latest company evidence submission. The updated analysis provided within the company submission aligns with that the committee made their original recommendation upon.
- Although a primary comparator, docetaxel is not the only relevant comparator for nivolumab, as patients may also receive methotrexate or another taxane (i.e. paclitaxel) in standard clinical practice. This was recognised in the original appraisal scope and also within the eligibility criteria for the managed access agreement, which included patients who "would otherwise be potentially fit for docetaxel-based or methotrexate-based 2nd line chemotherapy". The conclusion made by the committee in the original TA490 appraisal was that "docetaxel would be the most appropriate comparator *for people fit enough to have docetaxel*" (TA490 FAD; Section 3.2), and so it would be remiss to only focus on patients intended for docetaxel given the expected use of nivolumab for patients who might otherwise receive something other than docetaxel (i.e. methotrexate).

A2. Priority question. Page 10 of the company submission (CS) states: "No clinically meaningful relationship between body weight or nivolumab exposure or nivolumab exposure quartiles and frequency or severity of adverse events was observed. Based on consistent exposure-response relationships across indications, the benefit-risk profile of nivolumab 240 mg Q2W is likely to be similar to 3 mg/kg Q2W, therefore the clinical effectiveness of nivolumab that was demonstrated in CheckMate 141 (weight-based dose) is expected to be generalisable to the use of nivolumab in clinical practice (flat dose)." Please provide empirical evidence with references to support the claim that there will be no meaningful difference in either effectiveness or adverse event risk between the two methods of dosing, i.e. weight-based and flat dose.

The decision to switch from the weight-based dosing of nivolumab to a flat dose (across all licensed indications) was made by the European Medicines Agency (EMA) (Variation II/0036/G), with the flat dose of 240 mg once every two weeks (Q2W) now recommended as part of the licence for nivolumab in patients with recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN).[1, 2]

The 240 mg Q2W dose was chosen to approximate the exposures achieved with 3 mg/kg in patients weighing 80 kg, the median body weight of patients across nivolumab trials. Nivolumab

flat-dosing regimens are supported by well-established and robust population pharmacokinetic modelling and clinical safety data. Pharmacokinetics data in a simulated population of 3,458 patients with melanoma, renal cell carcinoma (RCC), SCCHN, squamous and non-squamous non-small cell lung cancer (NSCLC), urothelial carcinoma (UC), hepatocellular carcinoma (HCC), colorectal cancer (CRC), and gastric cancer (GC) showed that distributions of nivolumab exposures after 3 mg/kg Q2W and 240 mg Q2W were similar and below the exposures observed with 10 mg/kg Q2W. No clinically meaningful relationship between body weight or nivolumab exposure or nivolumab exposure quartiles and frequency or severity of adverse events (AEs) was observed. Based on flat exposure-response relationships across indications, the benefit-risk profile of nivolumab 240 mg Q2W is likely to be similar to 3 mg/kg Q2W.

A3. Priority question. Please provide all references included in the CS including the latest version of the clinical study report.

All references were provided as part of the company submission. A clinical study report was not generated for the latest data cut of the CheckMate 141 trial. Summary data in the form of Kaplan-Meier plots were provided as part of the reference pack in the absence of a full clinical study report.

A4. Priority question. Please provide a breakdown of age distribution in the CheckMate 141 using age categories reported for the Systemic Anti-Cancer Therapy (SACT) dataset (<40, 40-49, 50-59, 60-69, 70-79, 80+) for the full population and the subgroup of those eligible for docetaxel, both treated for the docetaxel and nivolumab.

The distribution of patients in the nivolumab arm of the CheckMate 141 trial to the age categories reported from the SACT data cohort are presented in Table 1.

Table 1: Age at baseline (by category) in the CheckMate 141 trial and SACT data cohort study

Age category, n (%)	CheckMate 141; Nivolumab (n=240)	SACT data cohort study (n=506)
<40	14 (6)	15 (3)
40-49	18 (8)	39 (8)
50-59	90 (38)	145 (29)
60-69	87 (36)	194 (38)
70-79	29 (12)	104 (21)
80+	2 (1)	9 (2)

Abbreviations: SACT: Systemic Anti-Cancer Therapy.
Sources: CheckMate 141 Data on File (15th October 2019), Public Health England report[3]

A5. Priority question. In Table 8 of the CS, the OS hazard ratios for nivolumab vs. IC are presented by PD-L1 subgroup.

a. Please present the hazard ratios for nivolumab vs. docetaxel for each of the PD-L1 subgroups.

b. Please present the results of a test of interaction by PD-L1 status for the hazard ratio.

c. Please also present equivalent results for PFS and TTD.

a.

As outlined in the response to Question A1, the 'docetaxel-only' comparison has not been conducted.

b.

Results of a test of interaction by PD-L1 status for the hazard ratio (HR) versus IC for overall survival (OS) have been conducted.

Cox proportional hazards models with treatment arm (reference: IC or nivolumab) and PD-L1 status (reference: PD-L1 <1% or PD-L1 ≥1% or PD-L1 not quantifiable) as covariates were performed with and without interaction between treatment arm and PD-L1 status. The results of these analyses are presented in Table 2 (Model 1; without interaction) and Table 3 (Model 2; with interaction). A comparison of the two models (Likelihood ratio test between Model 2 and Model 1; p=0.239) suggests that the simpler model (Model 1), without the interaction terms, is favoured.

In Model 1, the effect of treatment with nivolumab on OS, regardless of PD-L1 status, was reported as being statistically significant (p<0.001). In contrast, in Model 2, the effect of treatment with nivolumab on OS in patients with PD-L1 <1% was reported as being positive (HR<1), but not statistically significant (p=0.129). As outlined previously in the company evidence submission, the sample sizes in the PD-L1 subgroups are small (111 patients with PD-L1 <1%) and the resulting confidence intervals around the HR for nivolumab versus IC in the PD-L1 <1% subgroup are wide (HR: 0.741; 95% CI: 0.503, 1.091). Interpretation of analyses from the PD-L1 subgroups should therefore be done with caution. The HRs themselves do however indicate that treatment with nivolumab is of benefit when compared to IC in the PD-L1 <1% subgroup specifically (Model 2), and regardless of PD-L1 status (Model 1).

Table 2: Cox proportional hazards model for overall survival: without interaction (Model 1)

Variable	HR (exp[coefficient])	Lower 95% CI	Upper 95% CI	p-value
Treatment (nivolumab)	0.677	0.541	0.848	<0.001
PD-L1 ≥1%	1.093	0.859	1.391	0.470
PD-L1 not quantifiable	1.226	0.927	1.622	0.153

Likelihood ratio test = 12.49 on 3 degrees of freedom.
Abbreviations: CI: confidence intervals; HR: hazard ratio; PD-L1: programmed death ligand 1.

Table 3: Cox proportional hazards model for overall survival: with interaction (Model 2)

Variable	HR (exp[coefficient])	Lower 95% CI	Upper 95% CI	p-value
Treatment (nivolumab)	0.741	0.503	1.091	0.129
PD-L1 ≥1%	1.312	0.880	1.957	0.183
PD-L1 not quantifiable	1.056	0.617	1.809	0.842
Treatment (nivolumab)* PD-L1 ≥1%	0.750	0.454	1.239	0.261
Treatment (nivolumab)* PD-L1 not quantifiable	1.205	0.642	2.265	0.562

Likelihood ratio test = 15.35 on 5 degrees of freedom.
Abbreviations: CI: confidence intervals; HR: hazard ratio; PD-L1: programmed death ligand 1.

c.

Similarly, results of a test of interaction by PD-L1 status for the HR versus IC for progression-free survival (PFS; Table 4 and Table 5) and time to treatment discontinuation (TTD; Table 6 and Table 7) have also been conducted. The results of the Likelihood ratio test shows that the simpler model (without interaction terms) is favoured for PFS, but that Model 2 (with interaction) is favoured for TTD.

Table 4: Cox proportional hazards model for progression-free survival: without interaction (Model 1)

Variable	HR (exp[coefficient])	Lower 95% CI	Upper 95% CI	p-value
Treatment (nivolumab)	0.804	0.641	1.009	0.060
PD-L1 ≥1%	1.004	0.788	1.278	0.975
PD-L1 not quantifiable	1.201	0.908	1.591	0.200

Likelihood ratio test = 5.13 on 3 degrees of freedom.
Abbreviations: CI: confidence intervals; HR: hazard ratio; PD-L1: programmed death ligand 1.

Table 5: Cox proportional hazards model for progression-free survival: with interaction (Model 2)

Variable	HR (exp[coefficient])	Lower 95% CI	Upper 95% CI	p-value
Treatment (nivolumab)	1.043	0.707	1.537	0.833
PD-L1 ≥1%	1.413	0.947	2.109	0.091
PD-L1 not quantifiable	1.235	0.722	2.114	0.441
Treatment (nivolumab)* PD-L1 ≥1%	0.582	0.352	0.964	0.035
Treatment (nivolumab)* PD-L1 not quantifiable	0.921	0.490	1.729	0.797

Likelihood ratio test = 10.24 on 5 degrees of freedom.
Likelihood ratio test between Model 2 and Model 1; p= 0.0777
Abbreviations: CI: confidence intervals; HR: hazard ratio; PD-L1: programmed death ligand 1.

Table 6: Cox proportional hazards model for time to treatment discontinuation: without interaction (Model 1)

Variable	HR (exp[coefficient])	Lower 95% CI	Upper 95% CI	p-value
Treatment (nivolumab)	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 ≥1%	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 not quantifiable	[redacted]	[redacted]	[redacted]	[redacted]

Likelihood ratio test = 10.52 on 3 degrees of freedom.
Abbreviations: CI: confidence intervals; HR: hazard ratio; PD-L1: programmed death ligand 1.

Table 7: Cox proportional hazards model for treatment discontinuation: with interaction (Model 2)

Variable	HR (exp[coefficient])	Lower 95% CI	Upper 95% CI	p-value
Treatment (nivolumab)	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 ≥1%	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 not quantifiable	[redacted]	[redacted]	[redacted]	[redacted]
Treatment (nivolumab)* PD-L1 ≥1%	[redacted]	[redacted]	[redacted]	[redacted]
Treatment (nivolumab)* PD-L1 not quantifiable	[redacted]	[redacted]	[redacted]	[redacted]

Likelihood ratio test = 18.26 on 5 degrees of freedom.
Likelihood ratio test between Model 2 and Model 1; p= 0.0208
Abbreviations: CI: confidence intervals; HR: hazard ratio; PD-L1: programmed death ligand 1.

A6. Please provide adverse event data from the latest (15 October 2019) data cut-off as per the original submission? Were any new adverse events identified compared to the original submission?

The safety profile of nivolumab at the time of the latest data cut was consistent with previous data cuts of the CheckMate 141 trial. Data tables are provided in the reference pack which report AEs (all cause and drug-related) from the latest data cut and September 2016 data cut of CheckMate 141, with a summary of AEs provided below.[4, 5]

- In the latest data cut of the CheckMate 141 trial, the total number of all-cause AEs of any grade was the same as that reported in the data cut in the original submission (September 2016; provided ahead of the first Appraisal Committee Meeting for TA490), with 232 (98.3%) patients experiencing an event in the nivolumab arm and 109 (98.2%) in the IC arm.[4, 5] Similarly, the total number of drug-related AEs of any grade was the same in both data cuts, with 146 (61.9%) and 88 (79.3%) patients in the nivolumab and IC arms, respectively, experiencing an event.[4, 5]
- At the time of the latest data cut, the most frequently reported AEs (any grade) of any cause in the nivolumab arm were fatigue (67, 28.4%), nausea (50, 21.2%) and diarrhoea (44, 18.6%).[5] The same AEs were the most frequently reported at the time of the September 2016 data cut: fatigue (67, 28.4%), nausea (50, 21.2%) and diarrhoea (43, 18.2%).[4]
- The total number of all-cause AEs (Grade 3–4) in the latest data cut was 117 (49.6%) and 70 (63.1%) in the nivolumab and IC arms, respectively, compared to 113 (47.9%) for nivolumab and 69 (62.2%) for IC in the data cut of the original submission.[4, 5] Drug-related serious AEs (Grade 3–4) were also very similar between data cuts, with 37 (15.7%) and 41 (36.9%) events identified in the nivolumab and IC arms, respectively, compared to 36 (15.3%) and 40 (36.0%) in the September 2016 data cut.[4, 5]
- The most frequently reported AEs (Grade 3–4) of any cause in the nivolumab arm were anaemia (17, 7.2%), dyspnoea (13, 5.5%), hyponatraemia (13, 5.5%), pneumonia (12, 5.1%) and malignant neoplasm progression (11, 4.7%) at the time of the latest data cut off.[5] Again, the same AEs were the most frequently reported at the time of the September 2016 data cut: anaemia (15, 6.4%), dyspnoea (13, 5.5%), hyponatraemia (11, 4.7%), pneumonia (11, 4.7%) and malignant neoplasm progression (11, 4.7%).[4]

A7. There seems to be a discrepancy between the numbers in the CS. On page 11, the number of patients with known PD-L1 status is reported to be 260 (149 patients had PD-L1 expression ≥1% and 111 patients had PD-L1 expression <1%), but the numbers in Table 11 are [redacted] and [redacted] respectively. Please also check consistency with tables 9 and 10, and figures 9 and 10. Secondly, on p.11 it is reported that [redacted] patients ([redacted]) were still on treatment, but Table 11 refers to [redacted] patients ([redacted]). Could the company please resolve these discrepancies.

The data reported on page 11 of the company evidence submission is from an earlier data cut of the CheckMate 141 trial (interim analysis). The data reported on page 11 are accurate and are consistent with the data presented in the original publication for CheckMate 141.[6, 7] Since the interim analysis an additional 15 patients were identified as having tumour samples that were quantifiable for PD-L1 expression, and 2 patients who were originally classified as PD-L1 >=1%

have since been reclassified as PD-L1 not quantifiable. At the time of the latest data cut-off date (15th October 2019), the number of patients with PD-L1 ≥1%, PD-L1 <1% and PD-L1 not quantifiable was 157, 116 and 88, respectively, in the all randomised population (Tables 9 and 10 of the company evidence submission) and 153, 113 and 81, respectively, in the all treated population (Table 11 of the company evidence submission).

With regards to the second discrepancy, [redacted] and so is not captured in Table 11 of the company evidence submission.

Section B: Clarification on cost-effectiveness data

Population

B1. Priority question. As mentioned in question A1, the company has performed all clinical effectiveness analyses based on data from the whole CheckMate 141 trial population regardless of investigator's choice (IC). However, as outlined by NICE in the Terms of Engagement, docetaxel is the comparator of interest in the CDF review.

a. Please provide scenario analysis (and the accompanying model) informing all input parameters relevant for the cost-effectiveness analyses based on the clinical effectiveness results as requested in A1 of this clarification letter (i.e. those patients from CheckMate 141 who were randomised to docetaxel vs. those who would be eligible to receive docetaxel according to IC, but who were randomised to nivolumab).

b. Please provide detailed information on the estimation and justification of OS, PFS and TTD as used in the economic model for this specific subpopulation.

c. Please provide all the results of the analyses in the form that is presented in the CS using the subgroup of patients who were chosen to receive docetaxel (according to IC).

As outlined in the response to Question A1, the 'docetaxel-only' comparison has not been conducted.

Effectiveness

B2. Priority question. According to the Terms of engagement for CDF review "A piecewise model is expected to be used to extrapolation of OS in the CDF review". The company provided multiple methods to extrapolate OS in the economic model.

However, for the piecewise models, only exponential and lognormal distributions were explored.

a. Please provide scenario analysis (and the accompanying model) using different distributions for the piecewise models for the different cut-offs including the distributions the company explored for the standard parametric survival models to estimate and extrapolate OS.

b. Please provide detailed information on the selection of the most appropriate piecewise model to estimate and extrapolate OS.

c. Please also provide responses to sub-questions a and b using the subgroup of patients who were chosen to receive docetaxel (according to IC).

a.

The cost-effectiveness model has been updated to include piecewise analyses at various cut-off points (20 weeks, 36 weeks, 48 weeks and 96 weeks [overall population only]) for all distributions that were explored as part of fully parametric survival models.

The results of scenario analyses exploring alternative piecewise models are presented in Table 8 (overall population) and Table 9 (PD-L1 subgroups). As in the company evidence submission, piecewise analyses using the later cut-off points (48 weeks and 96 weeks) were primarily considered in order to maximise the use of the observed trial data.

As shown in part b) of this response, the exponential and lognormal distributions were amongst the 'best' fitting models (in terms of AIC and BIC) when compared to the other distributions. Inspection of the log cumulative hazard plot as part of the original evidence submission revealed a trend in the change in hazards over time with nivolumab which favours the use of the lognormal distribution over the exponential. Furthermore, the piecewise analyses using the exponential distribution tended to produce a poorer visual fit to the tail of the nivolumab curve across each of the populations (see part b) of this response). For these reasons, the piecewise analyses using the lognormal distribution are still considered to represent the most suitable distribution for extrapolating nivolumab OS. This is consistent with the conclusions made in the original TA490 appraisal that "the log normal distribution is more appropriate than the exponential distribution for the piecewise analysis" (TA490 FAD; Section 3.12).

Further details on how the piecewise analyses which have been explored below were selected are presented in part b) of this response.

In presenting cost-effectiveness results from the PD-L1 subgroups, it should again be noted that the results in the PD-L1 subgroup analyses should be treated with caution (due to the small sample sizes from which the data are derived), and that BMS believe that the evidence presented is such that nivolumab can be considered a cost-effective use of NHS resources in the overall population.

Overall population

Table 8: Piecewise scenario analyses (with PAS) versus docetaxel – overall population, flat dose

Scenario	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on base-case ICER
Base case	Piecewise lognormal 96-week cut-off for OS extrapolation	£37,236	-
Alternative piecewise model 1	Piecewise exponential 96-week cut-off for OS extrapolation	£45,182	+£7,946
Alternative piecewise model 2	Piecewise generalised gamma 96-week cut-off for OS extrapolation	£36,366	-£870
Alternative piecewise model 3	Piecewise lognormal 48-week cut-off for OS extrapolation	£40,167	+£2,931

Abbreviations: ICER: incremental cost effectiveness ratio; OS: overall survival; PAS: patient access scheme.

PD-L1 subgroups

Table 9: Piecewise scenario analyses (with PAS) versus docetaxel – PD-L1 subgroups, flat dose

Scenario	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on base-case ICER
PD-L1 <1%			
Base case	Piecewise lognormal 48-week cut-off for OS extrapolation	£46,309	-
Alternative piecewise model	Piecewise exponential 48-week cut-off for OS extrapolation	£54,543	+£8,234
PD-L1 ≥1%			
Base case	Piecewise lognormal 48-week cut-off for OS extrapolation	£36,163	-
Alternative piecewise model	Piecewise loglogistic 48-week cut-off for OS extrapolation	£35,706	-£457

Abbreviations: ICER: incremental cost effectiveness ratio; OS: overall survival; PAS: patient access scheme; PD-L1: programmed death ligand 1.

b.

The selection of the piecewise analyses that were explored in part a) of this response was based on consideration of statistical fit (AIC and BIC) and visual inspection of the how well the extrapolations matched the observed data. As only the later cut-off points for the piecewise analyses were considered, the fit of earlier cut-off points are not discussed here. Full details (i.e. AIC and BIC values; visual plots of the extrapolations versus the observed data) of these and all other analyses are available in the updated cost-effectiveness model – see 'OS' sheet for visual plots and 'OS raw data' sheet for AIC and BIC values.

The selection of piecewise analyses is described below for the overall population, with the information for each of the PD-L1 subgroups presented in the Appendix.

Overall population

A summary of goodness-of-fit data for the piecewise extrapolations of OS (Week 48 and Week 96) in the nivolumab and IC arms (overall population) is presented in Table 10. At the 96 week cut-off point, the distributions with the lowest AIC and BIC values are the exponential (nivolumab arm) and generalised gamma (IC arm). The lognormal distribution is the 2nd and 3rd best fitting distribution in the nivolumab arm and IC arm, respectively. At the 48 week cut-off point, the lognormal distribution is the associated with the lowest AIC and BIC values in both treatment arms.

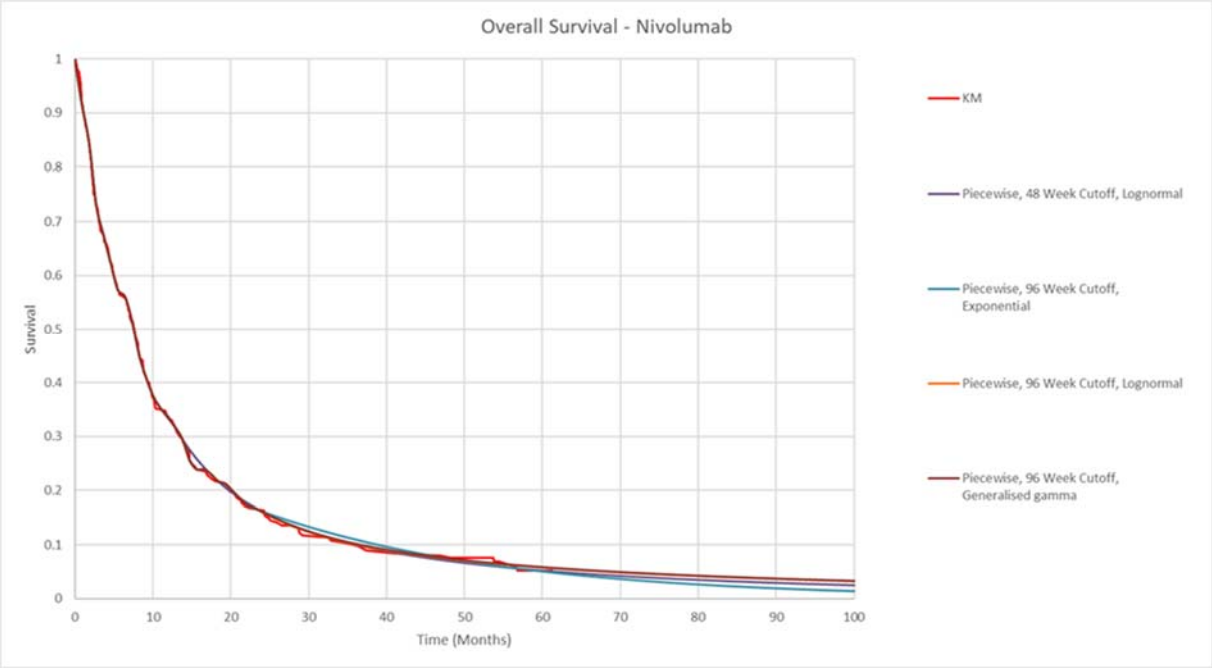
Visual inspection of each of these extrapolations (Week 96 exponential, Week 96 generalised gamma, Week 96 lognormal and Week 48 lognormal) shows that each distribution provides a reasonable fit to the observed data from the CheckMate 141 trial (see Figure 1), but the Week 96 exponential survival model provides a more pessimistic estimate of long-term survival and a poorer fit to the tail of the Kaplan-Meier curve compared to the other distributions.

Table 10: Summary of goodness-of-fit data for overall survival – overall population

Piecewise cut-off point:	48 weeks				96 weeks			
Distribution	Nivolumab		IC		Nivolumab		IC	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	719.166	721.573	217.152	218.288	285.075	286.713	65.328	65.274
Weibull	717.611	722.424	218.978	221.249	286.510	289.786	67.324	67.216
Log-Normal	**709.036**	**713.849**	**214.730**	**217.001**	**285.260**	**288.535**	**66.016**	**65.907**
Log-Logistic	711.242	716.056	215.689	217.960	285.800	289.075	66.520	66.412
Gamma	719.150	723.963	219.152	221.423	286.689	289.965	67.272	67.164
Gompertz	713.103	717.916	217.758	220.029	286.134	289.409	67.243	67.134
Generalised gamma	710.169	717.390	215.897	219.304	287.257	292.170	62.976	62.814

A smaller AIC or BIC value represents a better goodness of fit. Orange fill represents lowest AIC or BIC value. Lognormal (**bold**) was selected for the base case in the company evidence submission.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; IC: investigator's choice.

Figure 1: Long-term OS extrapolation using piecewise models for nivolumab (overall population)



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

c.

As outlined in the response to Question A1, the 'docetaxel-only' comparison has not been conducted.

B3. Priority question. The company states that "inspection of the log cumulative hazards plot shows that towards the end of the observed follow-up period of CheckMate 141 there is a difference between treatment arms in the change in hazard over time (see Figure 13), with a reduction in the hazard over time being observed in the nivolumab arm, compared to a relatively constant hazard in the IC arm. Should this trend continue beyond the 4-year follow-up period, it would not be appropriate to assume that the hazard in the nivolumab arm would be the same as the IC arm, as is done to model the treatment waning effect. Given the considerations outlined above, it is considered more plausible to predict long-term survival with nivolumab without applying the treatment waning effect at 5 years."
To support this claim and to assess the proportional hazards assumption,

a. Please provide a visual plot of the smoothed hazards over time for survival for both IC and nivolumab.

b. Please provide a visual plot of the log cumulative hazard over log time for survival for both IC and nivolumab.

c. Please provide a visual plot of scaled Schoenfeld residuals over time for survival for IC versus nivolumab.

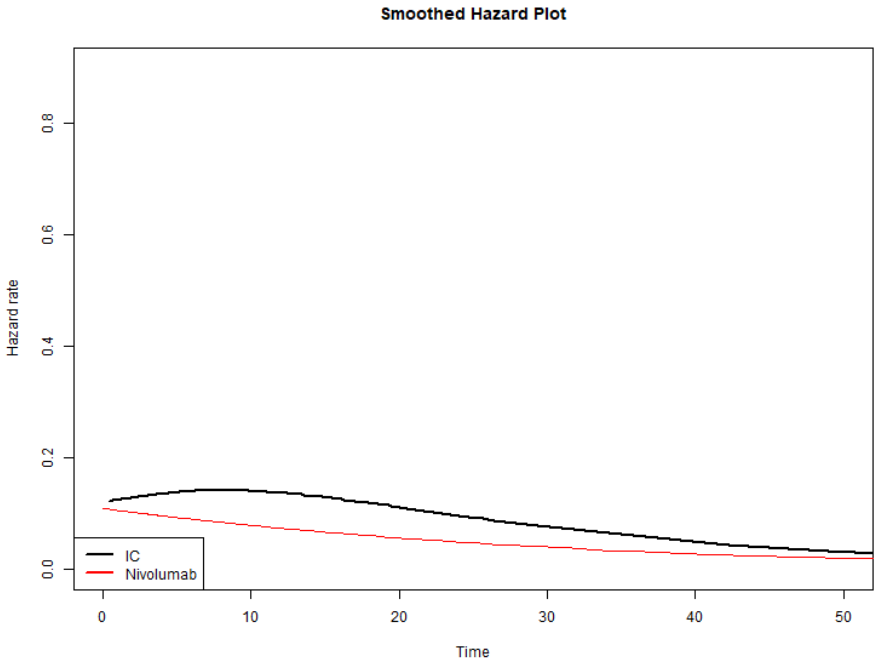
d. Please also provide responses to sub-questions a to c for PFS and TTD.

e. Please also provide responses to sub-questions a to d for the subgroups based on PD-L1 expression.

a.

A plot of smoothed hazards over time (in months) is presented in Figure 2 (nivolumab and IC; overall population). The decrease in hazards over time seen in the nivolumab arm is further supportive of the decision to favour the lognormal distribution over the exponential distribution (as per response to B2). The plot also shows the difference between IC and nivolumab in the change of hazards over time, with a steeper reduction in hazards being observed in the IC arm compared to the nivolumab arm. Should these trends continue, the application of the treatment waning assumption (in which it is assumed that the hazard of death would be the same in each treatment arm) at 5 years would not be considered appropriate.

Figure 2: Smoothed hazards plot for nivolumab and IC overall survival (overall population)



Abbreviations: IC: investigator's choice.

b.

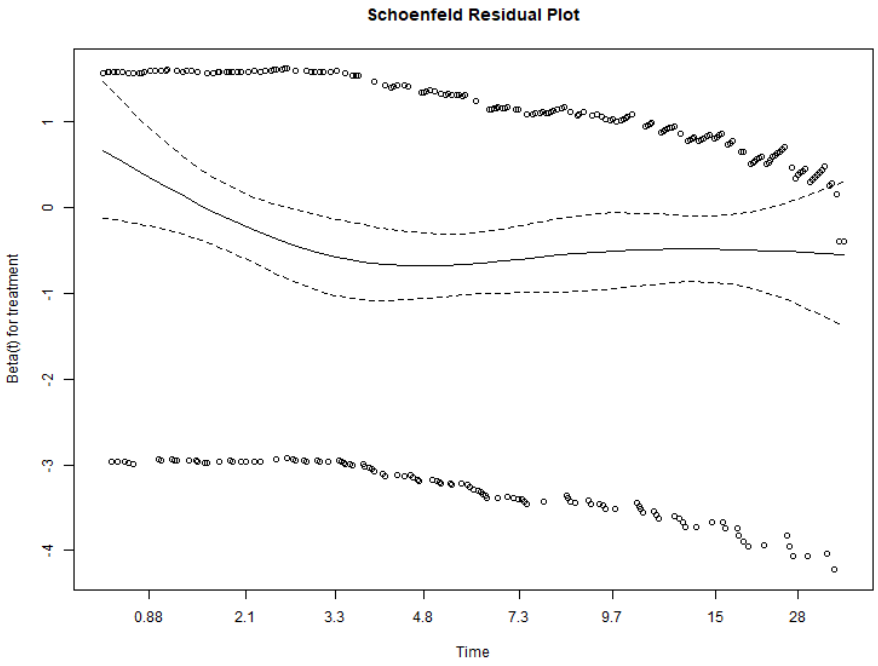
The plot provided in Figure 13 of the company evidence submission has been generated using a log scale for the x-axis (see cloglog function of plot.survfit in R package survival). The labelling on the x-axis is presented as time (months), rather than as log time, for ease of interpretation.

c.

A plot of Schoenfeld residuals over time is presented in Figure 3 (nivolumab and IC; overall population). The results of the Schoenfeld residuals test are not statistically significant

(p=0.0673), although as the mechanisms of action are different between chemotherapies and immuno-oncology drugs, it is expected that proportional hazards would not hold.

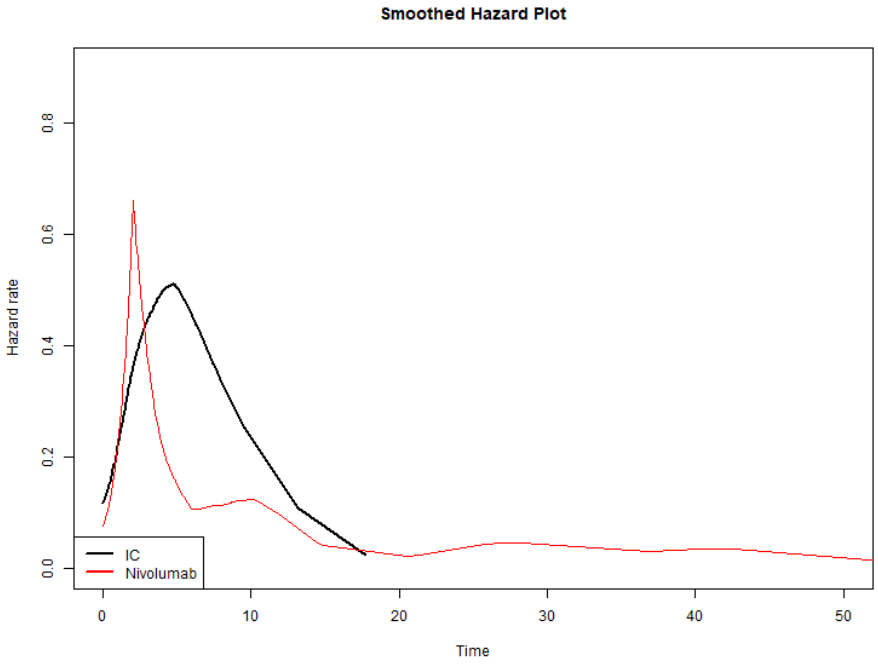
Figure 3: Schoenfeld residual plot for nivolumab and IC overall survival (overall population)



Abbreviations: IC: investigator's choice.

d. The relevant plots for PFS and TTD are presented below:

Figure 4: Smoothed hazards plot for nivolumab and IC progression-free survival (overall population)

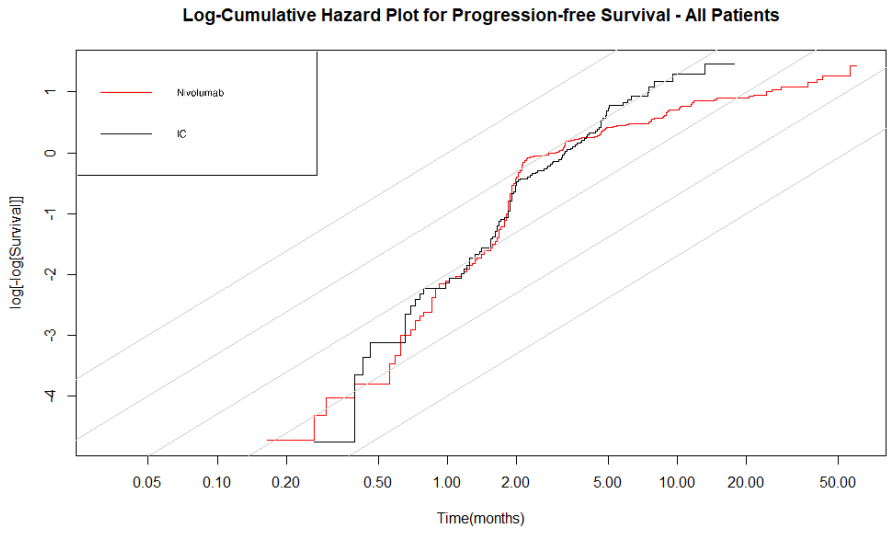


Abbreviations: IC: investigator's choice.

Figure 5: Smoothed hazards plot for nivolumab and IC time to treatment discontinuation (overall population)

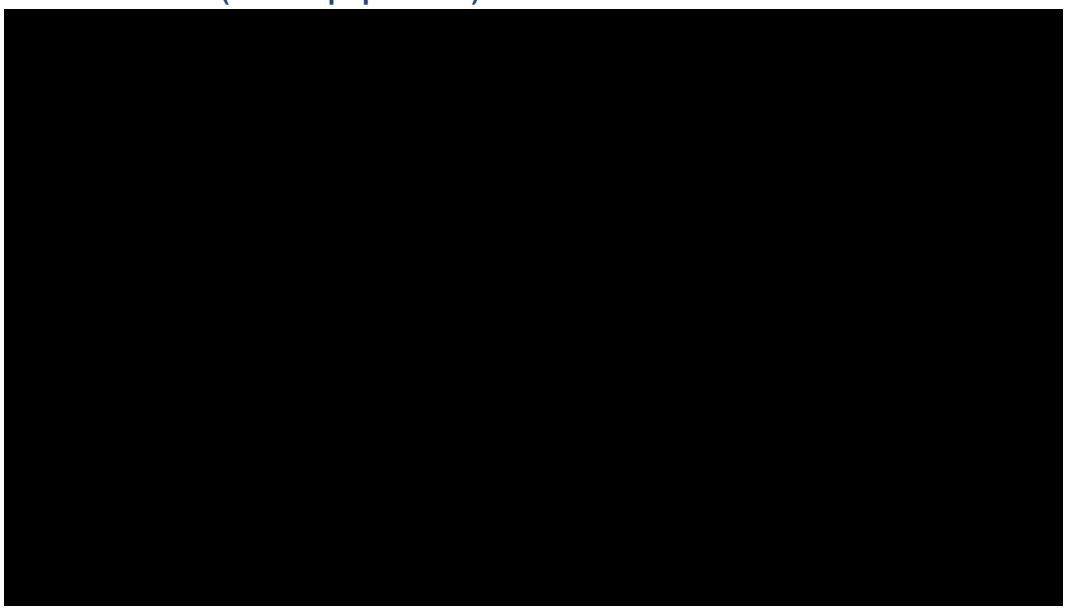
Abbreviations: IC: investigator's choice.

Figure 6: Log-cumulative hazards plot for nivolumab and IC progression-free survival (overall population)



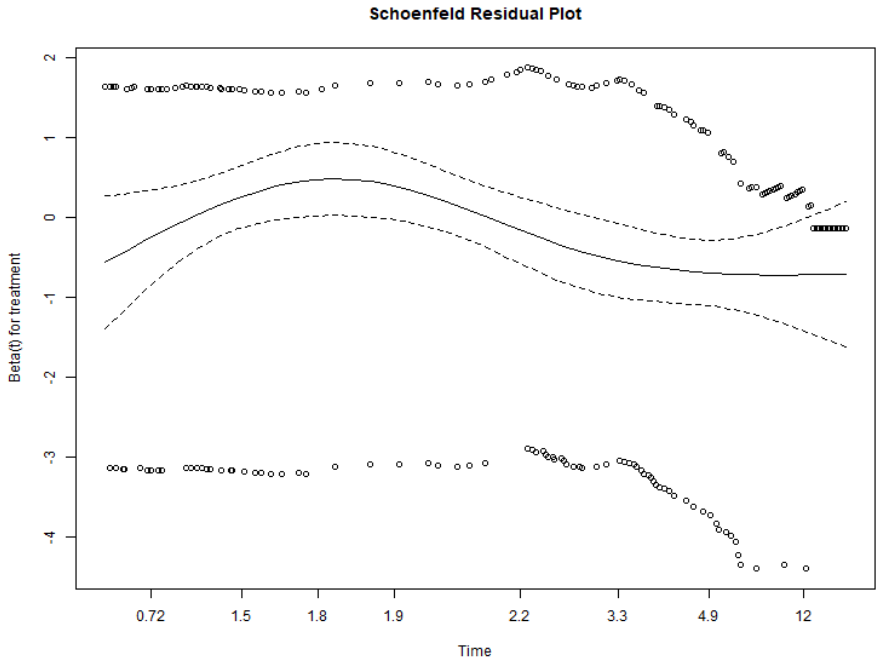
Abbreviations: IC: investigator's choice.

Figure 7: Log-cumulative hazards plot for nivolumab and IC time to treatment discontinuation (overall population)



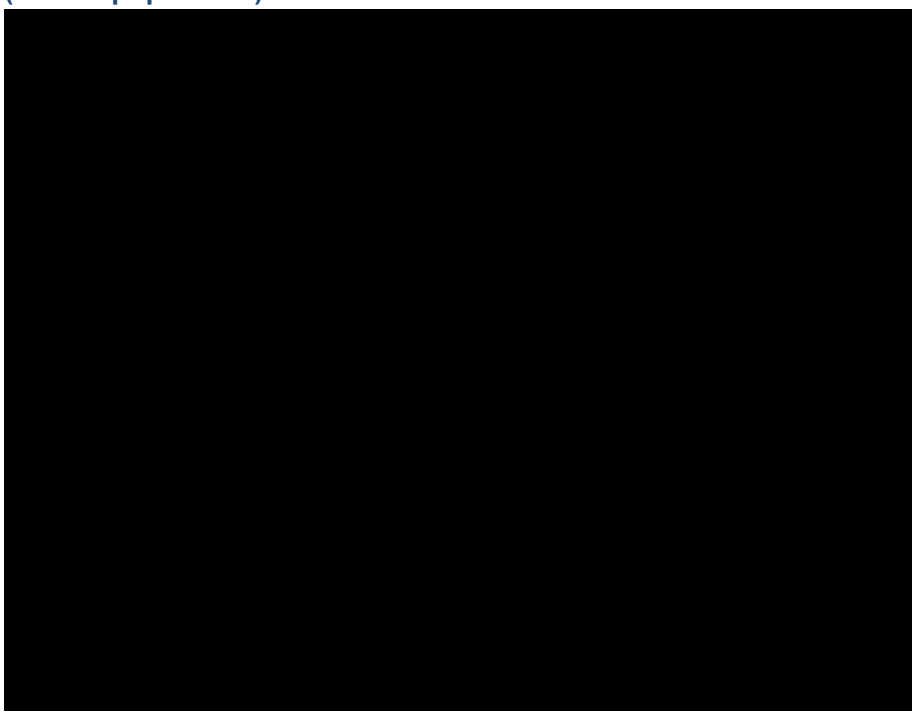
Abbreviations: IC: investigator's choice.

Figure 8: Schoenfeld residual plot for nivolumab and IC progression-free survival (overall population)



Schoenfeld residual test p= 0.0165
Abbreviations: IC: investigator's choice.

Figure 9: Schoenfeld residual plot for nivolumab and IC time to treatment discontinuation (overall population)



Schoenfeld residual test p<0.001
Abbreviations: IC: investigator's choice.

e.

The relevant plots for the PD-L1 subgroup analyses are presented in the Appendix.

B4. For TTD the company used the [redacted] for IC while parametric survival models were used for nivolumab.

a. Please justify this inconsistency between the estimation of TTD for IC and nivolumab and clarify whether this inconsistency might bias the results.

b. Please provide a scenario analysis using the company's preferred assumptions but consistently using parametric survival models for both IC and nivolumab.

a. Extrapolation of data in the model was only carried out for instances where not all events had occurred. For TTD in the nivolumab arm [redacted]. The 2 spline normal model was therefore chosen for extrapolation as the model provided the best statistical fit and a reasonable visual fit to the observed data. The 2 spline model also predicted a reasonable estimate of mean TTD when compared to PFS (i.e. mean TTD and mean PFS were similar). However, for the IC arm, [redacted] in the CheckMate 141 trial at the time of the latest data cut-off. [redacted]

b. Results from a scenario analysis using the company's base case assumptions with the 2 spline odds model used to extrapolate TTD for both IC and nivolumab is presented in Table 11.

The 2 spline odds model was chosen for the extrapolation of both nivolumab and IC, as the 2 spline normal model, which was used in the base case analysis for the extrapolation of nivolumab TTD, provides a poor visual fit for IC. In contrast, the 2 spline odds model produces the 2nd best statistical fit for nivolumab (according to AIC and BIC), is amongst the highest ranked models for IC (see Table 12), and also provides a reasonable visual fit for both arms (see Figure 10 and Figure 11).

Table 11: Cost-effectiveness analysis 3: Parametric scenario analysis (with PAS) – overall population, flat dose

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	£10,555	0.67	0.35	[redacted]	0.65	[redacted]	£36,745
Paclitaxel	£11,989	0.67	0.35	[redacted]	0.65	[redacted]	£33,689
Methotrexate	£11,606	0.67	0.35	[redacted]	0.65	[redacted]	£34,504

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

Table 12: Summary of goodness-of-fit data for time to treatment discontinuation (overall population)

Distribution	Nivolumab		IC	
	AIC	BIC	AIC	BIC
Exponential	1239.736	1243.200	419.022	421.732
Weibull	1183.841	1190.768	418.167	423.587
Log-Normal	1182.226	1189.154	458.579	463.998
Log-Logistic	1160.668	1167.596	439.908	445.327
Gamma	1202.061	1208.988	419.407	424.826
Gompertz	1164.232	1171.159	418.815	424.234
Generalised gamma	1171.362	1181.753	419.038	427.167
1-Spline Hazard	1167.889	1178.281	416.997	425.126
2-Spline Hazard	1152.755	1166.611	411.662	422.500
1-Spline Odds	1155.359	1165.751	413.240	421.369
2-Spline Odds	1148.706	1162.561	414.945	425.784
1-Spline Normal	1166.073	1176.464	413.987	422.115
2-Spline Normal	1147.494	1161.349	434.917	445.755

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; IC: investigator's choice.

Figure 10: Long-term TTD extrapolation using parametric models for nivolumab (overall population)

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

Figure 11: Long-term TTD extrapolation using parametric models for IC (overall population)

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

B5. Appendix B provides visual plots of the KM curves and parametric survival models. In addition, goodness-of-fit data are summarised in a table. However, this information is missing for TTD for the PD-L1 <1% subgroup. Please provide for the PD-L1 <1% subgroup, the visual plots of the KM curves and parametric survival models as well as the goodness-of-fit data for TTD (consistent with the reporting used in Appendix B).

The visual plots of the Kaplan-Meier curves and parametric survival models, alongside goodness-of-fit data were not presented for TTD for the PD-L1 <1% subgroup as, similar to the IC arm in the overall population, [redacted]). It was therefore not considered necessary to provide this information. Goodness-of-fit data and the visual plots (nivolumab and IC) have been provided here as requested in Table 13 and Figure 12 and Figure 13, respectively.

Table 13: Summary of goodness-of-fit data for time to treatment discontinuation (PD-L1 <1%)

Distribution	Nivolumab		IC	
	AIC	BIC	AIC	BIC
Exponential	372.696	375.000	167.034	168.698
Weibull	367.723	372.331	167.801	171.128
Log-Normal	365.298	369.906	180.353	183.681
Log-Logistic	357.779	362.387	171.449	174.776
Gamma	371.248	375.856	167.945	171.272
Gompertz	362.022	366.630	168.473	171.800
Generalised gamma	363.601	370.513	169.800	174.790
1-Spline Hazard	361.395	368.307	169.608	174.598
2-Spline Hazard	359.192	368.409	167.844	174.498
1-Spline Odds	358.682	365.594	166.443	171.433
2-Spline Odds	357.682	366.898	168.035	174.689
1-Spline Normal	362.587	369.499	167.055	172.045
2-Spline Normal	356.984	366.200	169.906	176.560

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PD-L1: programmed death ligand 1.

Figure 12: Long-term TTD extrapolation of parametric models for nivolumab (PD-L1 <1%)

Abbreviations: KM: Kaplan-Meier; PD-L1: programmed death ligand 1; TTD: time-to-treatment discontinuation.

Figure 13: Long-term TTD extrapolation of parametric models for IC (PD-L1 <1%)

Abbreviations: IC: investigator's choice; KM: Kaplan-Meier; PD-L1: programmed death ligand 1; TTD: time-to-treatment discontinuation.

B6. Compared with the CheckMate 141 trial, the SACT data provides real-world data that might better reflect UK clinical practice.

a. Please provide a scenario analysis (and the accompanying model) using the SACT data to estimate OS for nivolumab.

b. Please provide a scenario analysis (and the accompanying model) using the SACT data to estimate time to TTD for nivolumab (if needed assuming PFS is equal to TTD to prevent logical inconsistencies).

a.

The use of OS data from the SACT cohort for the cost-effectiveness model has been explored as part of this response. Pseudo individual patient-level data, derived using digitised Kaplan-Meier plots from the Public Health England report and the approach described by Guyot *et al.* (2012), were first extrapolated using standard parametric approaches and a piecewise approach (Week 20 cut-off point only).[8]

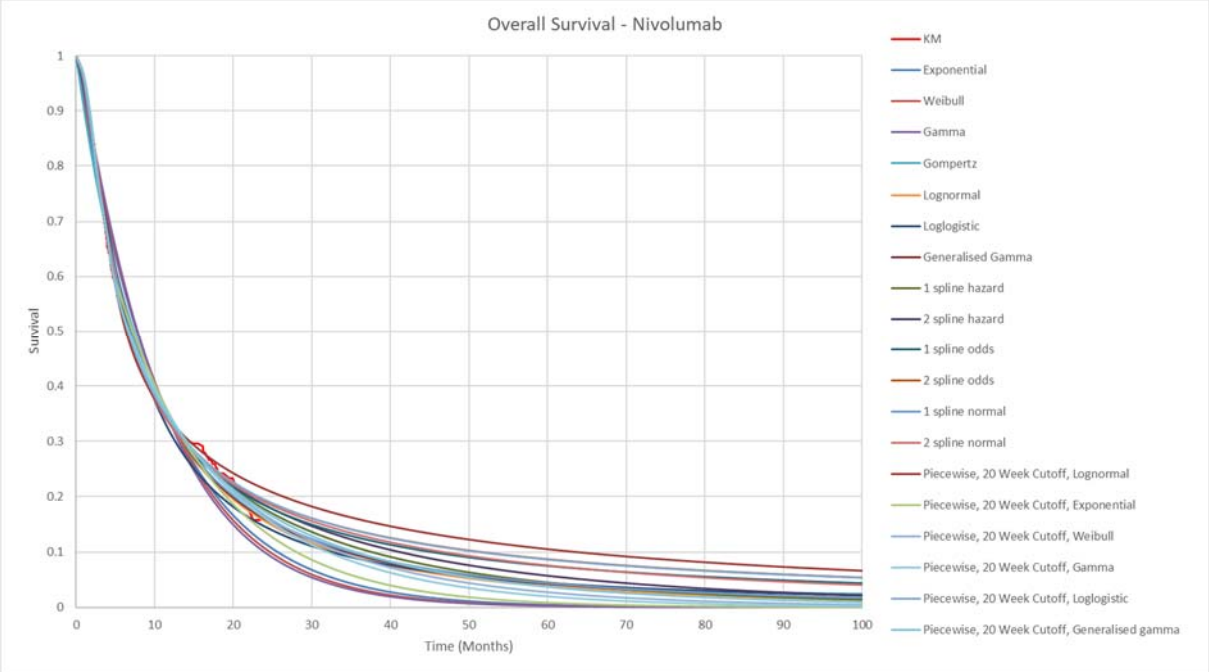
As shown in Figure 14, there is a range of possible extrapolations for OS using the SACT data – each with varying estimates of long-term OS. Of the various distributions explored for the piecewise analyses, the Weibull was associated with lowest AIC and BIC values, with the loglogistic (which produces a similar curve to the lognormal) being the 3rd 'best' fitting distribution (see Table 10).

Table 14: Summary of goodness-of-fit data for overall survival – SACT

Piecewise cut-off point:	20 weeks	
Distribution	Nivolumab	
	AIC	BIC
Exponential	1430.092	1433.792
Weibull	1424.845	1432.246
Log-Normal	1434.069	1441.470
Log-Logistic	1426.295	1433.696
Gamma	1425.269	1432.670
Gompertz	1427.168	1434.569
Generalised gamma	1426.620	1437.721

A smaller AIC or BIC value represents a better goodness of fit. Orange fill represents lowest AIC or BIC value.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; IC: investigator's choice.

Figure 14: Long-term OS extrapolation using standard parametric and piecewise models for nivolumab (SACT)



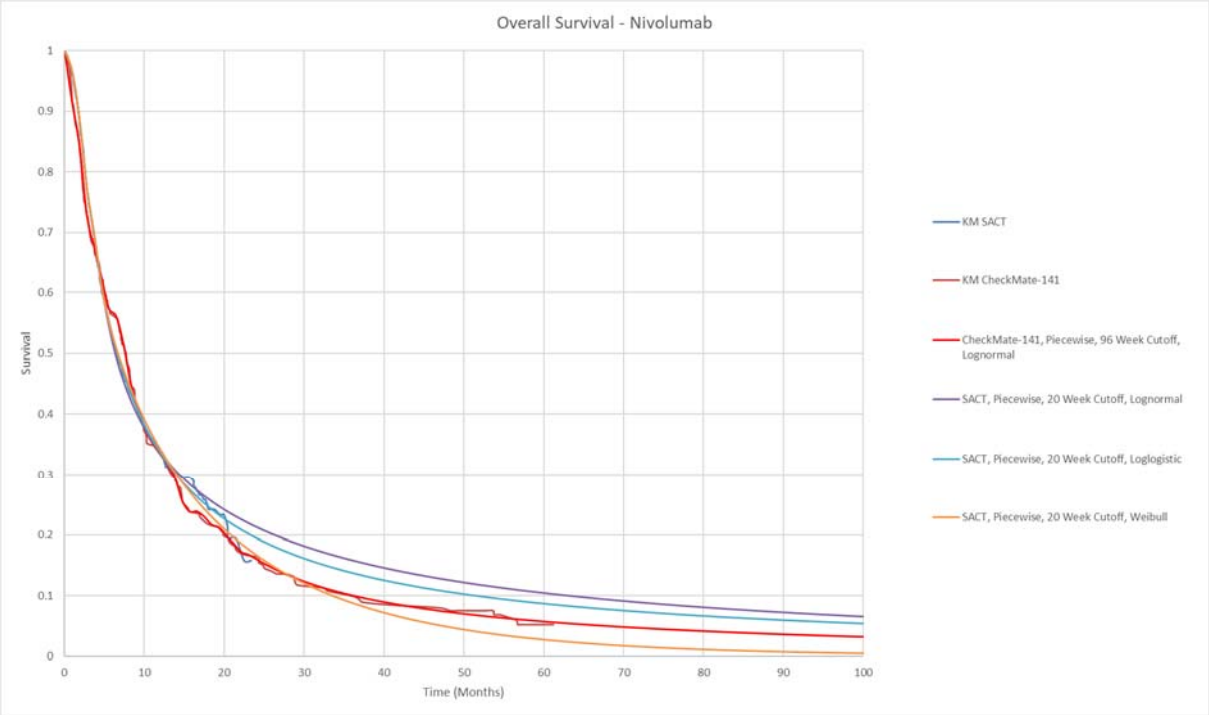
Abbreviations: KM: Kaplan-Meier; OS: overall survival.

As shown in the company evidence submission, the observed OS in the SACT cohort was consistent with the CheckMate 141 trial for the duration of the SACT follow-up. However, when compared to observed data from CheckMate 141 trial, the Weibull, loglogistic and lognormal piecewise extrapolations of the SACT data produce estimates of OS that are very dissimilar to the outcomes from the longer-term follow-up of the CheckMate 141 trial (see Figure 15): the Weibull extrapolation underestimates OS, whereas the loglogistic and lognormal extrapolations both overestimate OS when compared to the CheckMate 141 data. With the expectation of a long tail in the survival curve for nivolumab (as seen in the longer-term follow-up of the CheckMate 141 trial), the data from the SACT cohort are potentially too immature to be able to accurately capture the potential long-term survival outcomes with nivolumab.

The use of OS data from SACT would therefore only increase the uncertainty in the cost-effectiveness analysis. With the availability of more mature data from the CheckMate 141 trial and the need to address uncertainty in the long-term survival benefits of nivolumab as part of this

CDF review, the OS data from the SACT cohort is not considered to be informative for decision making and so has not been incorporated in the updated cost-effectiveness model.

Figure 15: Long-term OS extrapolation using Week 20 piecewise analyses: Weibull, loglogistic and lognormal (SACT) compared to CheckMate 141 observed data and extrapolation



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

b.

The use of TTD data from the SACT cohort for the cost-effectiveness model has also been explored as part of this response, with a similar process used to that described for OS (with the exception that no piecewise analyses were explored for the extrapolation of TTD, as per the approach taken using data from CheckMate 141).

Unlike OS, TTD data from the SACT cohort has been incorporated into the cost-effectiveness model. Uncertainty in the long-term extrapolation of TTD is largely mitigated by the inclusion of the 2-year stopping rule in the base case analysis, and so the relative immaturity of the SACT TTD data is less of a concern. TTD in the SACT cohort was generally higher than that observed in the CheckMate 141 trial, as shown in the company evidence submission. The use of TTD data from the SACT cohort in the cost-effectiveness analysis therefore produces a higher estimate of the ICER than the base case analysis (i.e. using data from CheckMate 141) due to the increased costs related to treatment that are accrued in the nivolumab arm.

Given that disease progression will be the reason to stop treatment for a high proportion of patients, it is expected that TTD would be similar to PFS. In the cost-effectiveness model, PFS has therefore been assumed to be equivalent to TTD when the TTD data from SACT are used in the model (rather than being modelled using data from CheckMate 141). This is considered necessary given the aforementioned difference in TTD from SACT versus TTD (and PFS) from CheckMate 141.

Of the various models explored to extrapolate TTD from SACT, the 1 spline hazards model was associated with the lowest BIC value and produced a curve with a reasonable fit to the observed data (see Table 15 and Figure 16). Cost-effectiveness results using TTD from SACT (1 spline

hazards) for nivolumab TTD and PFS, with all other inputs and assumptions the same as Cost-effectiveness analysis 3, are presented in Table 16.

Table 15: Summary of goodness-of-fit data for time to treatment discontinuation – SACT

Distribution	Nivolumab	
	AIC	BIC
Exponential	2129.935	2134.161
Weibull	2131.388	2139.841
Log-Normal	2048.499	2056.952
Log-Logistic	2049.912	2058.365
Gamma	2130.775	2139.228
Gompertz	2099.619	2108.072
Generalised gamma	2040.671	2053.351
1-Spline Hazard	2027.877	2040.556
2-Spline Hazard	2028.309	2045.215
1-Spline Odds	2029.076	2041.755
2-Spline Odds	2028.203	2045.109
1-Spline Normal	2039.005	2051.684
2-Spline Normal	2027.416	2044.322

A smaller AIC or BIC value represents a better goodness of fit. Orange fill represents lowest AIC or BIC value.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; IC: investigator's choice.

Figure 16: Long-term TTD extrapolation using parametric and spline models for nivolumab (SACT)

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

Table 16: SACT TTD scenario analysis (with PAS) versus docetaxel – overall population, flat dose

Scenario	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on base-case ICER
Base case	TTD and PFS extrapolated using data from CheckMate 141	£37,236	-
SACT TTD	TTD extrapolated using data from SACT (1 spline hazards) and PFS assumed to be equivalent to TTD	£51,434	+£14,198

Abbreviations: ICER: incremental cost effectiveness ratio; PAS: patient access scheme; PFS: progression-free survival; TTD: time to treatment discontinuation.

Health related quality of life

B7. Priority question. In the CS the company states that no further analyses to those conducted in TA490 were undertaken to estimate utility based on progression status. The company did, however, apply decrements in utility based on time to death.

a. Please clarify why the updated data from the CheckMate 141 trial was not used to recalculate utilities based on progression status?

b. Please provide updated utilities based on progression status using the data from the CheckMate 141 trial (data cut-off: 15th October 2019). Specifically, using approaches preferred by the committee; NICE guidance for TA490 states that "it [the committee] accepted the company's preferred approaches for estimating treatment-dependent utilities (model 6) and treatment-independent utilities (model 7)".

c. Please also provide responses to sub-question b using the subgroup of patients who were chosen to receive docetaxel (according to IC).

a.

The additional analyses of utility that were conducted in the company evidence submission were based on the EQ-5D data used in the original appraisal. These were conducted to specifically address the concerns raised about modelling changes in utility over time.

Collection of additional EQ-5D data was not included as part of the data collection agreement on entry into the CDF, and the use of EQ-5D from the latest data cut of the CheckMate 141 was not explored as part of the company evidence submission. Within the timeframe permitted for this

response, it has not been possible to re-analyse utility values using EQ-5D data from the latest data cut.

Information on completion rates and the number of observations collected at the time of the latest data cut of the CheckMate 141 trial have however been provided as part of the reference pack.[9] Whilst the number of observations has increased since the earlier data cut, there were very few additional observations in the IC arm ([redacted]) and at Week 57, [redacted] in the nivolumab arm were still in the study and able to complete an EQ-5D questionnaire.

b.

Not applicable based on response to part a).

c.

Not applicable based on response to part a).

B8. In the Terms of engagement for CDF review NICE stated that it expected the quality of life benefit to not remain constant over time. The company tried to address this by applying decrements in utility based on the proportion of patients who are predicted to die within the next three model cycles (so last three months only).

a. In table 12 of the CS the mean estimates of utility by time to death are presented. Given the relatively large mean difference in utility between 3-6 months ([redacted]) and 0-3 months [redacted]) to death the ERG is not convinced that utility decrements should be applied to the last three months only. Please justify the approach used by the company; specifically: i) why the period of 3 (or 6 months) is used and; ii) why time before death is used instead of time since start (or stopping) treatment to implement quality of life benefits related to treatment that are not constant over time.

b. Please provide a breakdown of utilities from 3 to 6 months before death in the same way as is done for 0-3 months to death, i.e. as in Table 15.

c. Please add a scenario in which utilities decrements are applied from 6 months to death onwards i.e. separately decrements applied based on whether patients are one, two, three, four, five or six cycles from death.

a.

i. Decrements in utility beyond the three cycles before death were not applied, as analyses of EQ-5D data from CheckMate 141 showed that changes in utility were most apparent in the three months prior to death. Compared to 3–6 months from death ([redacted]) and 6+ months from death ([redacted]), which showed relatively similar utility values between the two periods, and also with the values already used for utility in the PD

health state ([redacted] in the treatment-independent scenario), the 0–3 month time period ([redacted]) resulted in the largest change in utility.

ii. Time to death was used instead of time since the start (or stopping) of treatment as the last few months of life is where the greatest loss of health-related quality of life (HRQoL) is expected to occur. This is supported by the findings from the time-to-death utility analysis using data from the CheckMate 141 trial, which showed a lower utility in the 0–3 months prior to death compared to earlier time intervals (see response to part a.i)). It is also practically difficult to model the change in utility over multiple cycles from time of progression using the existing model structure, as it is not possible to track patients post-progression over time and know when each patient will experience death. Death, on the other hand, is an absorbing health state in the model from which time can easily be fixed for the proportion of patients experiencing the event in a given cycle.

b.

The EQ-5D data from the CheckMate 141 trial has been reanalysed to estimate utility in 28-day cycles for time-to-death from 0–28 days to 141–183 days (>6 months). The results of this analysis are presented in Table 17 alongside the size of the decrements in utility that would be applied in the model.

Table 17: Time-to-death utility values and decrements

Utility value	Treatment-dependent		Treatment-independent
	Nivolumab	IC	Both treatment arms
Progressed disease	[redacted]	[redacted]	[redacted]
Time to death			
Six model cycles (141–183 days)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]
Five model cycles (113–140 days)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]
Four model cycles (85–112 days)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]
Three model cycles (57–84 days)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]
Two model cycles (29–56 days)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]
One model cycle (0–28 days)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]

[a] As the time-to-death utility is greater than the PD utility, no decrement would be applied.
Abbreviations: IC: investigator's choice.

c.

As shown in Table 17, the size of the decrements in utility to be applied in the model for 85–183 days before death are relatively small and in a number of cases (e.g. in the IC arm, when using treatment-dependent utility values) no additional decrements would be applied.

To provide a crude estimate of the likely impact of including these additional utility decrements (for 85–183 days before death) on cost-effectiveness results, an exploratory analysis has been conducted in which these decrements are all applied together in the third cycle before death (i.e. for the treatment-dependent scenario, the utility decrement in the third model cycle from death is [redacted] for IC and [redacted] for nivolumab). This approach does not account for the possible effect of discounting when applying the decrements across multiple cycles in the model, but does provide a close approximation of what the ICER might be, with minimal changes required to the programming of the model.

Using this approach and otherwise keeping the same assumptions as Cost-effectiveness analysis 3, the ICER versus docetaxel is £37,597 per QALY gained, compared to £37,236 per QALY gained in the original base case (time-to-death utility in 0–3 months prior to death). As such, it is not expected that extending the time period over which utility decrements are applied will have a considerable impact on the cost-effectiveness results.

Resources and costs

B9. As per TA490, the company implemented a 2-year stopping rule. Sensitivity analyses presented in Table 22 of the CS indicate that the inclusion of this stopping rule has a high impact on the company's base-case ICER.

a. Please explain the high impact of the stopping rule in the base-case ICER given that at 24 months only a small proportion ([redacted]) of patients in the nivolumab arm were still on treatment.

The application of the stopping rule only impacts the costs associated with nivolumab in the model. The disaggregated costs from Cost-effectiveness analysis 3 (with and without the application of the 2-year stopping rule) are presented in Table 18, and these show that the main difference between the scenarios is the costs associated with treatment acquisition (as well as administration and monitoring). This difference in costs between the two scenarios is equivalent to the 'average' patient receiving an additional three doses of nivolumab (over 6 weeks) in the without stopping rule scenario. In the model, a proportion of patients (albeit small) continue to receive nivolumab for several months and years when the stopping rule is not applied, which accounts for the increase in treatment-related costs and changes in cost-effectiveness results.

Table 18: Disaggregated costs in the nivolumab arm (with and without stopping rule)

	With stopping rule	Without stopping rule
Total	[redacted]	[redacted]
PF	[redacted]	[redacted]
PD	[redacted]	[redacted]
One-off progression	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]
Treatment monitoring	[redacted]	[redacted]

Subsequent treatments (total)	[redacted]	[redacted]
Adverse events	£467	£467

Abbreviations: PD: progressed disease; PF: progression free.

B10. According to Table 13 of the CS, the PD-L1 score for patients was not recorded for 42% (n=210) of the SACT data cohort study population. This could indicate that testing for PD-L1 expression is not part of usual care for treating recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) patients within the UK population. This would mean that if nivolumab would only be accepted for treating patients according to their PD-L1 expression level, additional testing on PD-L1 expression would be required, which will lead to additional costs related to nivolumab.

a. Could the company please provide information on the quantification of PD-L1 expression in current clinical practice in adult patients with recurrent or metastatic SSCHN in the UK. More specifically, could the company justify whether testing for PD-L1 expression in adult patients with recurrent or metastatic SSCHN is part of usual care in the UK population.

b. Please provide the costs associated with a PD-L1 test.

c. Please provide scenario analyses, for the PD-L1 subgroups, in which PD-L1 costs are incorporated. Note that these costs should include the number of individuals tested but not treated with nivolumab.

(a–c)

PD-L1 testing is standard clinical practice in the UK, when required.

As part of the managed access agreement for entry into the CDF, PD-L1 testing was required because the NICE committee concluded it was plausible that nivolumab has a different level of clinical effectiveness according to PD-L1 expression. As detailed in Section 5.4 of the managed access agreement, the company were advised that this test will be paid for by NHS England.

The reason for including PD-L1 testing in the managed access agreement was to supplement the trial data in the PD-L1 subgroups. The testing was not conducted to determine which patient may receive nivolumab, as the reimbursement criteria was based on prior platinum treatment only. The number of patients that had a score not recorded in the SACT database indicates that clinicians are willing to prescribe nivolumab to all patients, suggesting that they believe nivolumab is of benefit regardless of PD-L1 status, and are not concerned that there may be different levels of clinical effectiveness according to PD-L1 expression.

As shown in the company evidence submission, the 4-year data from CheckMate 141 demonstrated that nivolumab was associated with a numerical improvement in OS compared to

the IC arm, with considerable overlap between the 95% confidence intervals for the HRs for nivolumab versus IC from the PD-L1 <1% and ≥1% subgroups. As such there is not sufficient evidence that there is a statistically significant difference between these subgroups in terms of OS. Therefore, nivolumab should continue to be reimbursed in the overall population, as per the licensed indication.

Validity

B11. The economic model submitted by the company contains multiple references to external files (starting with "**='S:\Clients\BMS\I-O**"). Please provide a functioning economic model without external links.

A revised economic model will be submitted alongside this document in which references to external files are removed from any cells and 'buttons' where these have been identified.

B12. As stipulated in the Terms of Engagement, the company should provide a replication of the key cost-effectiveness results used in the committee's decision-making at the point of CDF entry. In the CS, the company states that the cost-effectiveness results at entry to the CDF have been replicated in **Error! Reference s ource not found.** of the CS (Cost-effectiveness analysis 1) with all model inputs and parameters (aside from a change in dosing schedule from weight-based to flat dosing) unchanged from the original cost-effectiveness analysis. It is, however, not clear to the ERG how the parameters in the revised model should be amended in order to replicate the original ICERs.

a. The ICERs reported in Table 17 of the CS and table 15 of appendix D do not appear to be in line with the ICERs reported in the Final Appraisal Document or Terms of Engagement for nivolumab compared with docetaxel (i.e. these ICERs do not range between either £45,000 and £73,600 or, as per the commercial access agreement, £30,377 and £49,408 per quality-adjusted life year gained). Please explain why the estimates appear to be not in line and present results that are in line with those mentioned in the Terms of Engagement.

b. Please provide a detailed breakdown of the required steps to replicate the ICERs used in committee's decision-making at the point of CDF entry (and reported in the Terms of Engagement) when using the revised health economic model. Provide in your answer a detailed overview of which cells to amend in the model and which parameters/settings are chosen for the various

input parameters (e.g. distributions for survival curves, treatment waning, choice of population, dosing regimen).

c. Please provide an economic model with the ability implemented to replicate the cost-effectiveness results at entry to the CDF with all model inputs and parameters unchanged from the original cost-effectiveness analysis.

a.

ICERs in Table 15 of Appendix D (weight-based dose) are with [redacted]% PAS and with a 2-year stopping rule applied

- The difference between these and the range of ICERs reported in the Terms of Engagement (£30,377 and £49,408 per QALY gained) is the application of the higher [redacted]% PAS discount
- The difference between these and the range of ICERs reported in the FAD (£45,000 and £73,600 per QALY gained; which are rounded to the nearest £100) is the exclusion of the 2-year stopping rule

b.

To replicate the analysis with an ICER of £30,377 per QALY gained (lognormal piecewise 36 week cut-off point; treatment-specific utility) from the cost-effectiveness analysis 3 (revised base case analysis), the following steps are required in the model:

Sheet	Cell range	Description	Value
Settings	G69	Time-to-death disutility included	No
	G71	Flat 240 mg dose nivolumab	No
OS	G6	Patient sample	Full sample (2 year data)
	H11	Curve to be fitted to Nivolumab arm	Waning treatment effect
	H13	Curve to be fitted to comparator arm	Piecewise, 36 Week Cutoff, Lognormal
	DT36	With treatment waning effect: curve selection	Piecewise, 36 Week Cutoff, Lognormal
TTD	K8	Curve to be fitted for Nivolumab TTD	Generalised gamma
	M428	Curve to be fitted to Investigator's Choice TTD	Generalised gamma
Treatment costs	L22 and L23	Nivolumab discount	[redacted]%

Abbreviations: OS: overall survival; TTD: time to treatment discontinuation.

To replicate the analysis with an ICER of £44,957 per QALY gained (£45,000 to the nearest £100; lognormal piecewise 36 week cut-off point; treatment-specific utility) from the cost-effectiveness analysis 3 (revised base case analysis), the following steps are required in the model:

Sheet	Cell range	Description	Value
Settings	G69	Time-to-death disutility included	No
	G71	Flat 240 mg dose nivolumab	No
OS	G6	Patient sample	Full sample (2 year data)
	H11	Curve to be fitted to Nivolumab arm	Waning treatment effect
	H13	Curve to be fitted to comparator arm	Piecewise, 36 Week Cutoff, Lognormal
	DT36	With treatment waning effect: curve selection	Piecewise, 36 Week Cutoff, Lognormal
TTD	K8	Curve to be fitted for Nivolumab TTD	Generalised gamma
	M428	Curve to be fitted to Investigator's Choice TTD	Generalised gamma
Treatment costs	G110	Apply a Clinical Stopping Rule	No

Abbreviations: OS: overall survival; TTD: time to treatment discontinuation.

c.

Replication of the cost-effectiveness results at entry to the CDF can be achieved by following the steps outlined in Question B12 part b) in the economic model provided alongside the company evidence submission.

Sensitivity analyses

B13. Could you provide sensitivity analyses for "Cost-effectiveness analysis 2" (updated committee preferred base-case), in alignment with those presented for "Cost-effectiveness analysis 3" (revised base-case).

Results from probabilistic and deterministic sensitivity analyses are presented below for Cost-effectiveness analysis 2. These are presented for both 'treatment-specific' and 'treatment-independent' utility scenarios, but only for the 48-week cut-off point for the lognormal piecewise analyses.

Probabilistic Sensitivity Analysis

Piecewise lognormal 48-week cut off, treatment-specific utility values

The results of the probabilistic sensitivity analysis (PSA) for Cost-effectiveness analysis 2, using the piecewise lognormal 48-week cut off and treatment-specific utility values, are provided in Table 19. A scatter plot of the incremental costs and QALYs for nivolumab (with PAS) versus docetaxel is presented in Figure 17. Assuming a willingness-to-pay threshold of £50,000 per QALY gained, the probability of nivolumab being the most cost-effective treatment option was 55.7% (with the PAS applied). The cost-effectiveness acceptability curves for nivolumab (with PAS) versus all comparators are presented in Figure 18.

Table 19: Cost-effectiveness analysis 2 results (average probabilistic) – piecewise lognormal 48-week cut off, overall population, flat dose

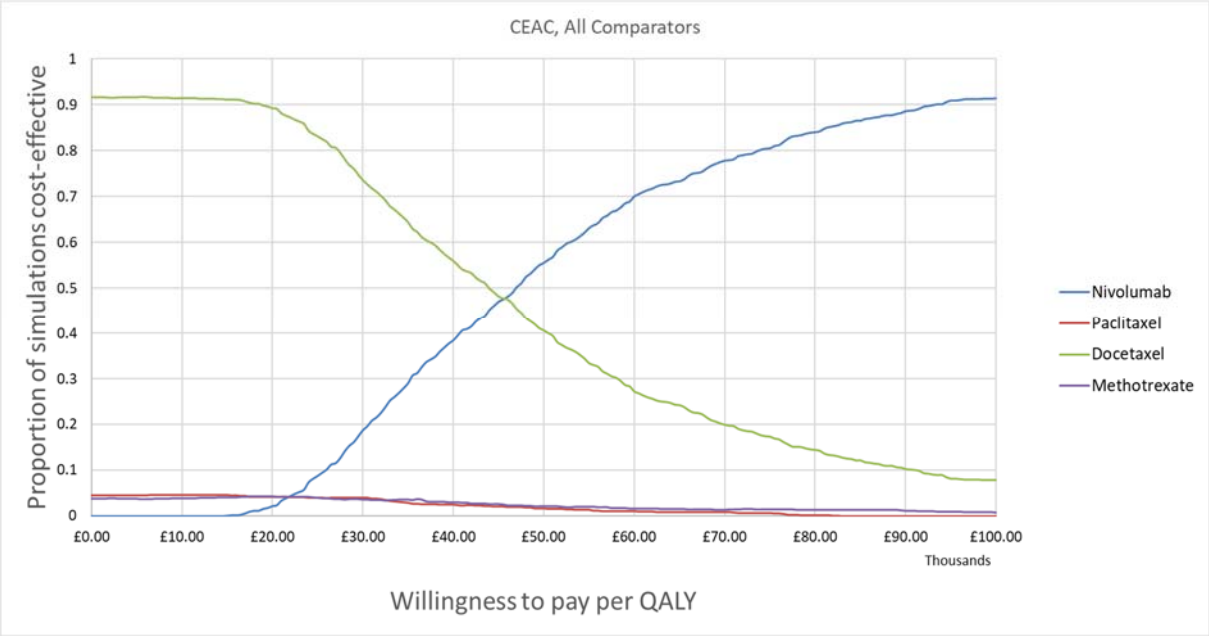
Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,530	0.37	[redacted]	[redacted]	£44,070
Paclitaxel	£11,955	0.37	[redacted]	[redacted]	£40,681
Methotrexate	£11,561	0.37	[redacted]	[redacted]	£41,622

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

Figure 17: Cost-effectiveness plane for nivolumab (with PAS) versus docetaxel – Cost-effectiveness analysis 2, piecewise lognormal 48-week cut off, overall population, flat dose

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 18: Cost-effectiveness acceptability curve for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate – Cost-effectiveness analysis 2, piecewise lognormal 48-week cut off, overall population, flat dose



Abbreviations: CEAC: cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Piecewise lognormal 48-week cut off, treatment-independent utility values

The results of the probabilistic sensitivity analysis (PSA) for Cost-effectiveness analysis 2, using the piecewise lognormal 48-week cut off and treatment-independent utility values, are provided in Table 20. A scatter plot of the incremental costs and QALYs for nivolumab (with PAS) versus docetaxel is presented in Figure 19. Assuming a willingness-to-pay threshold of £50,000 per QALY gained, the probability of nivolumab being the most cost-effective treatment option was 42.4% (with the PAS applied). The cost-effectiveness acceptability curves for nivolumab (with PAS) versus all comparators are presented in Figure 20.

Table 20: Cost-effectiveness analysis 2 results (average probabilistic) – piecewise lognormal 48-week cut off, overall population, flat dose

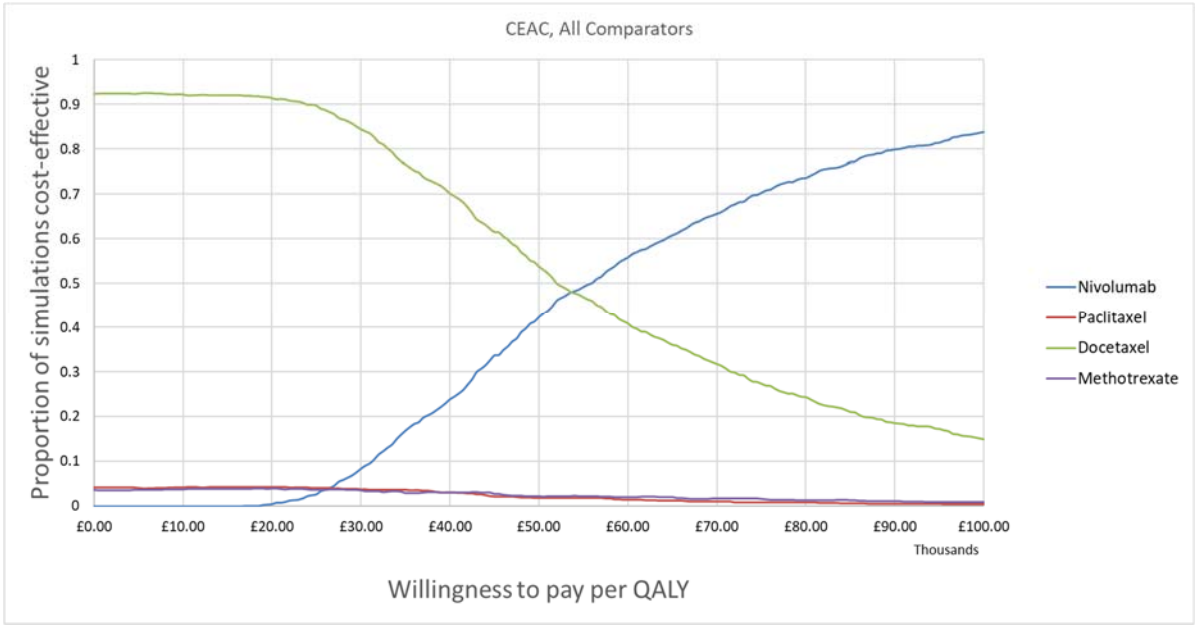
Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,527	0.41	[redacted]	[redacted]	£54,171
Paclitaxel	£11,960	0.41	[redacted]	[redacted]	£50,038
Methotrexate	£11,560	0.41	[redacted]	[redacted]	£51,187

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

Figure 19: Cost-effectiveness plane for nivolumab (with PAS) versus docetaxel – Cost-effectiveness analysis 2, piecewise lognormal 48-week cut off, overall population, flat dose

Abbreviations: PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 20: Cost-effectiveness acceptability curve for nivolumab (with PAS) versus docetaxel, paclitaxel and methotrexate – Cost-effectiveness analysis 2, piecewise lognormal 48-week cut off, overall population, flat dose



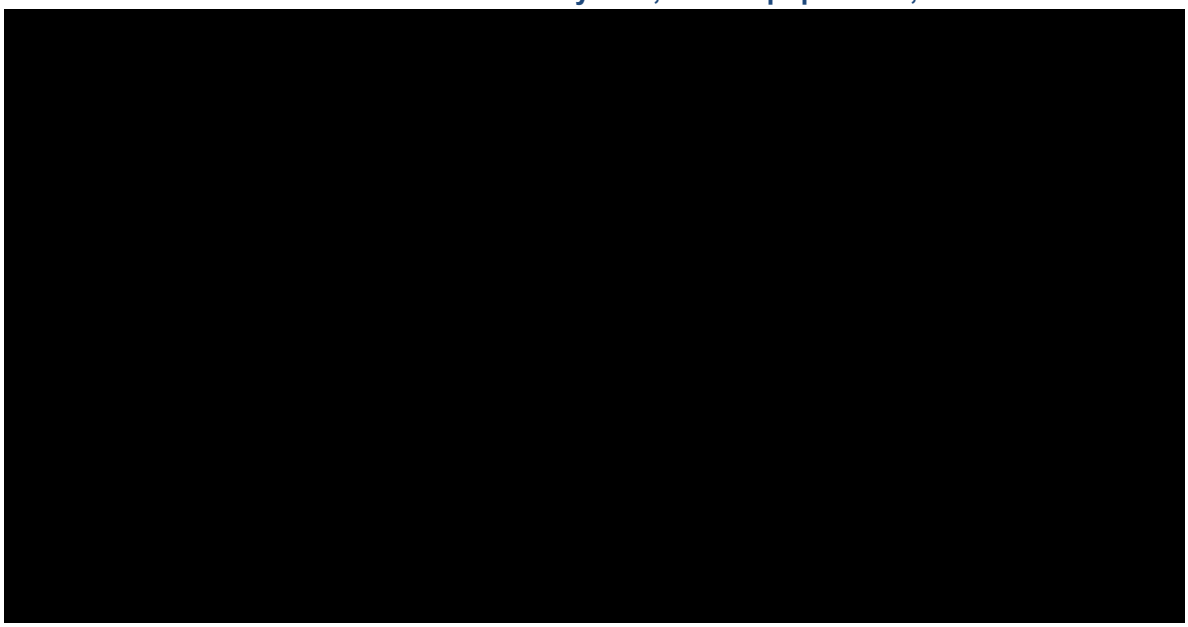
Abbreviations: CEAC: cost-effectiveness acceptability curve; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Deterministic Sensitivity Analysis

Piecewise lognormal 48-week cut off, treatment-specific utility values

A tornado diagram showing the top ten drivers of cost-effectiveness in the comparison of nivolumab versus docetaxel in Cost-effectiveness analysis 2, when nivolumab is provided with the PAS discount, is presented in Figure 21.

Figure 21: Tornado diagram of the ten most influential parameters: nivolumab (with PAS) versus docetaxel – Cost-effectiveness analysis 2, overall population, flat dose

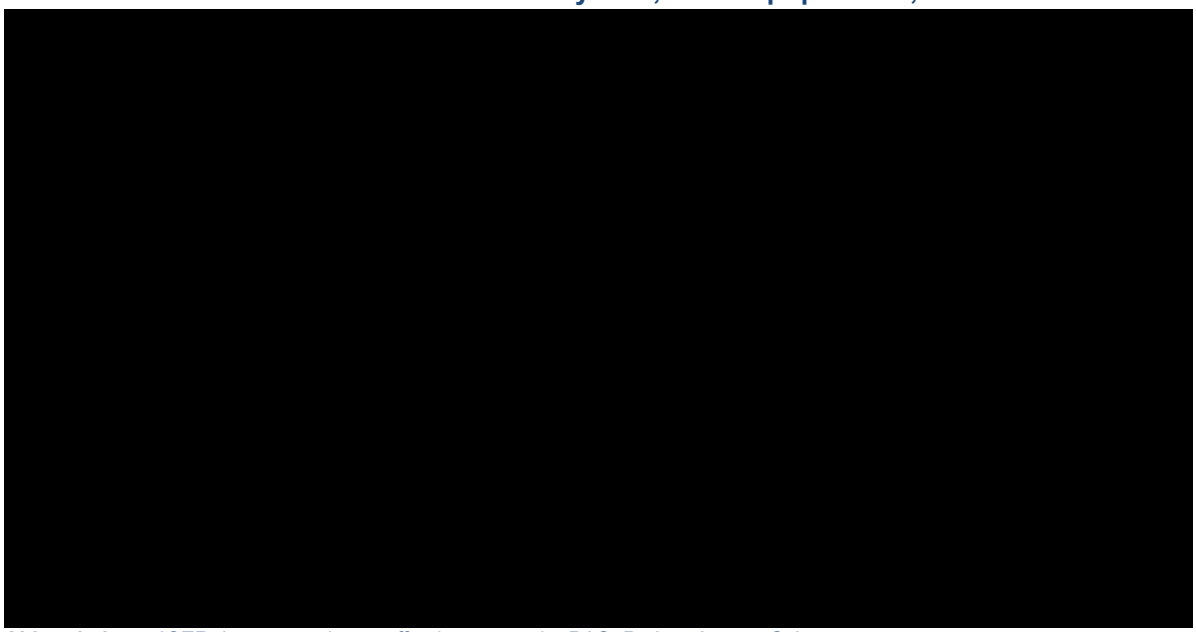


Abbreviations: ICER; incremental cost-effectiveness ratio; PAS; Patient Access Scheme.

Piecewise lognormal 48-week cut off, treatment-independent utility values

A tornado diagram showing the top ten drivers of cost-effectiveness in the comparison of nivolumab versus docetaxel in Cost-effectiveness analysis 2, when nivolumab is provided with the PAS discount, is presented in Figure 22.

Figure 22: Tornado diagram of the ten most influential parameters: nivolumab (with PAS) versus docetaxel – Cost-effectiveness analysis 2, overall population, flat dose



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

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Appendix

B2.

b.

PD-L1 <1% subgroup

A summary of goodness-of-fit data for the piecewise extrapolations of OS (Week 48 only) in the nivolumab arm (PD-L1 <1% subgroup) is presented in Table 21. As per the approach used in the company evidence submission, extrapolation of data in the IC arm was considered unnecessary, as all events had occurred in PD-L1 <1% patients in the IC arm at the time of the latest data cut.

The distribution with the lowest AIC and BIC values was the exponential and was followed by the lognormal distribution as the 2nd best fitting distribution.

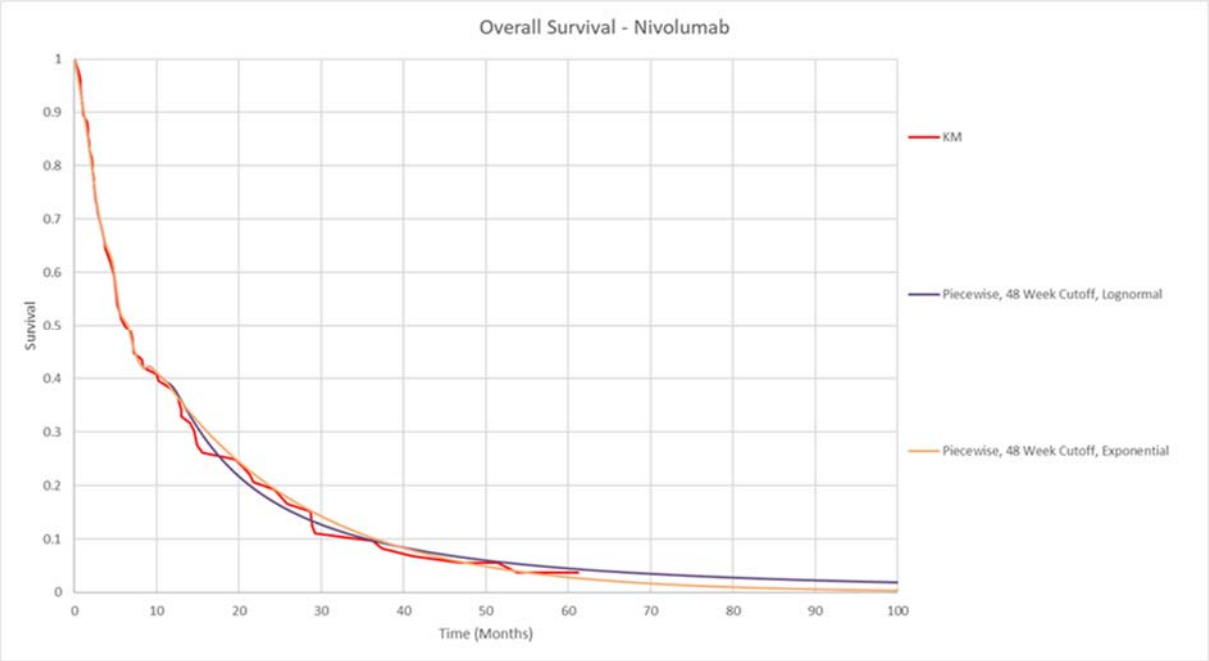
Visual inspection of Week 48 exponential and Week 48 lognormal show that both distributions provide a reasonable fit to the observed data (see Figure 23), but as per the overall population, the exponential distribution produces a more pessimistic estimate of long-term survival and a poorer fit to the tail of the Kaplan-Meier curve.

Table 21: Summary of goodness-of-fit data for overall survival – PD-L1 <1%

Piecewise cut-off point:	**48 weeks**	
Distribution	**Nivolumab**	
	AIC	**BIC**
Exponential	282.214	283.615
Weibull	284.065	286.868
Log-Normal	**282.815**	**285.617**
Log-Logistic	283.796	286.598
Gamma	284.171	286.973
Gompertz	283.688	286.490
Generalised gamma	284.762	288.966

A smaller AIC or BIC value represents a better goodness of fit. Orange fill represents lowest AIC or BIC value. Lognormal (**bold**) was selected for the base case in the company evidence submission.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PD-L1: programmed death ligand 1.

Figure 23: Long-term OS extrapolation using piecewise models for nivolumab (PD-L1 <1%)



Abbreviations: KM: Kaplan-Meier; OS: overall survival; PD-L1: programmed death ligand 1.

PD-L1 ≥1% subgroup

A summary of goodness-of-fit data for the piecewise extrapolations of OS (Week 48 only) in the nivolumab arm (PD-L1 ≥1% subgroup) is presented in Table 21. As per the approach used in the company evidence submission, extrapolation of data in the IC arm was considered unnecessary, as all events had occurred in PD-L1 ≥1% patients in the IC arm at the time of the latest data cut.

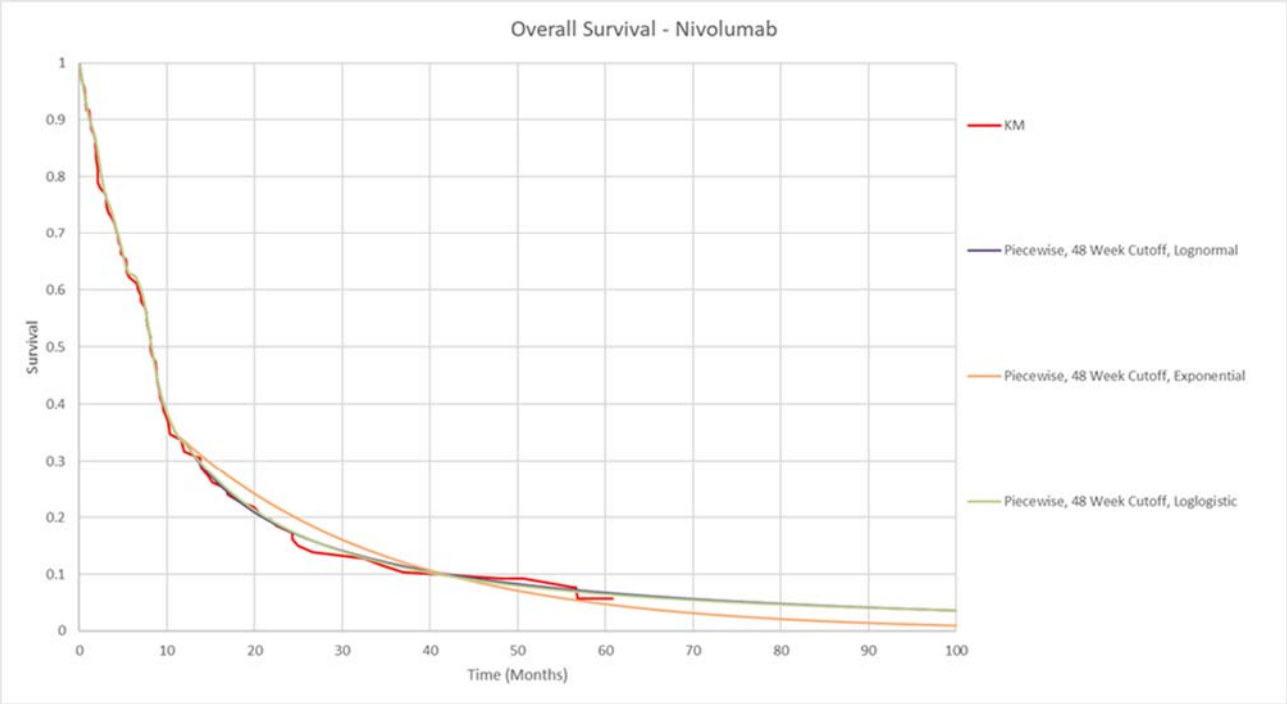
The distribution with the lowest AIC value was the lognormal, whereas the exponential distribution was associated with the lowest BIC value. Similarly to the lognormal distribution, the loglogistic was associated with low AIC and BIC values relative to the other distributions. Visual inspection of the plots for these three distributions shows that Week 48 lognormal and Week 48 loglogistic distribution provide similar and reasonable fits to the observed data (see Figure 24), whereas the exponential distribution is associated with a poor fit to the Kaplan-Meier curve. A scenario analysis using the exponential distribution was therefore not explored.

Table 22: Summary of goodness-of-fit data for overall survival – PD-L1 ≥1%

Piecewise cut-off point:	**48 weeks**	
Distribution	**Nivolumab**	
	AIC	**BIC**
Exponential	285.226	286.722
Weibull	285.873	288.866
Log-Normal	**284.461**	**287.454**
Log-Logistic	284.843	287.837
Gamma	286.265	289.258
Gompertz	285.256	288.249
Generalised gamma	286.435	290.924

A smaller AIC or BIC value represents a better goodness of fit. Orange fill represents lowest AIC or BIC value. Lognormal (**bold**) was selected for the base case in the company evidence submission.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PD-L1: programmed death ligand 1.

Figure 24: Long-term OS extrapolation using piecewise models for nivolumab (PD-L1 ≥1%)



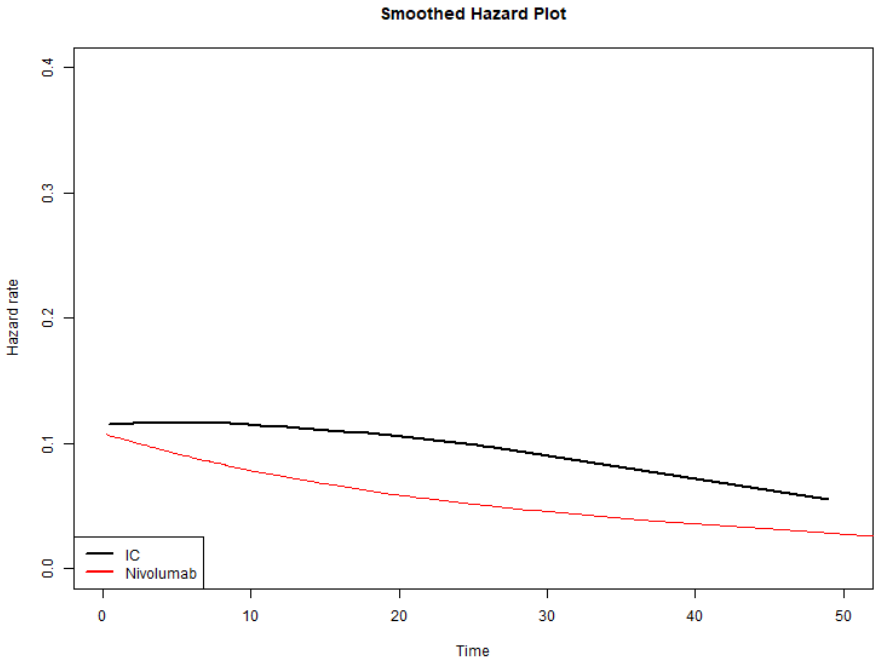
Abbreviations: KM: Kaplan-Meier; OS: overall survival; PD-L1: programmed death ligand 1.

B3.

e.

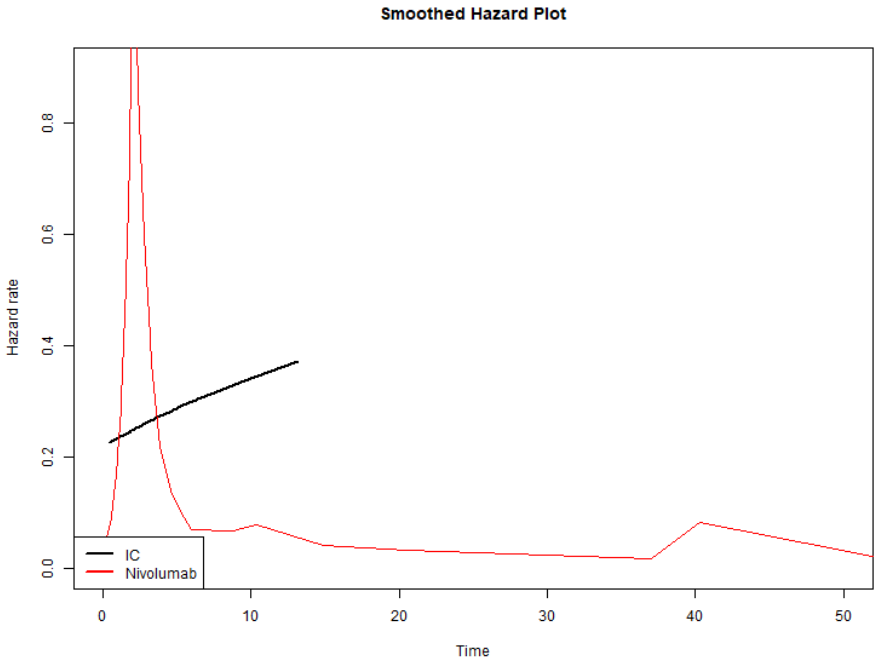
PD-L1 <1%

Figure 25: Smoothed hazards plot for nivolumab and IC overall survival (PD-L1 <1%)



Abbreviations: IC: investigator's choice.

Figure 26: Smoothed hazards plot for nivolumab and IC progression-free survival (PD-L1 <1%)



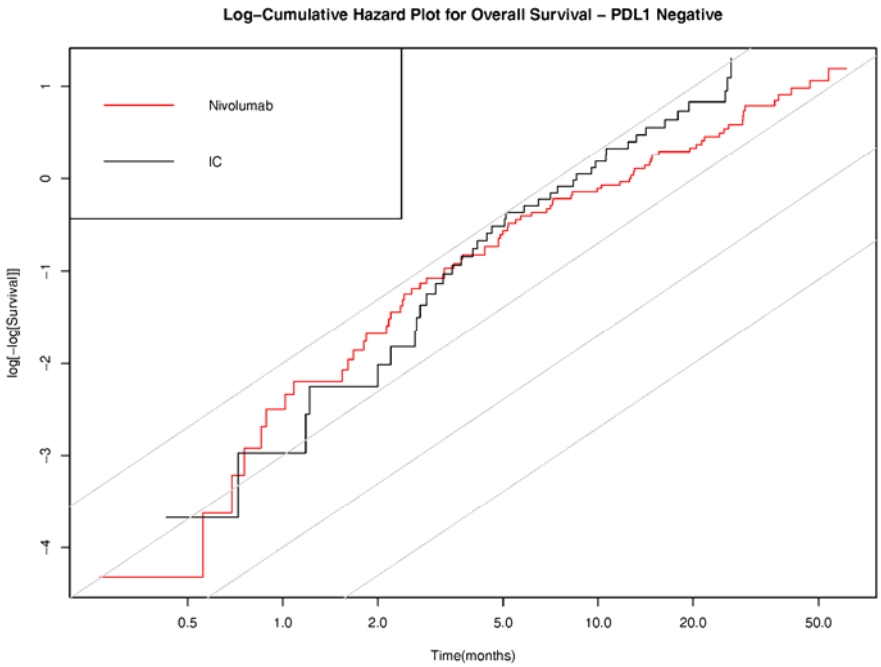
Abbreviations: IC: investigator's choice.

Figure 27: Smoothed hazards plot for nivolumab and IC time to treatment discontinuation (PD-L1 <1%)

[redacted]

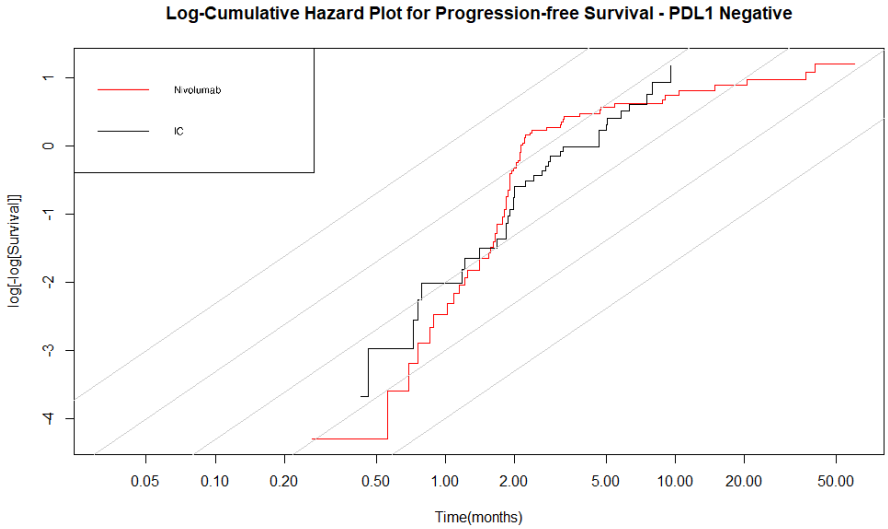
Abbreviations: IC: investigator's choice.

Figure 28: Log-cumulative hazards plot for nivolumab and IC overall survival (PD-L1 <1%)



Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

Figure 29: Log-cumulative hazards plot for nivolumab and IC progression-free survival (PD-L1 <1%)

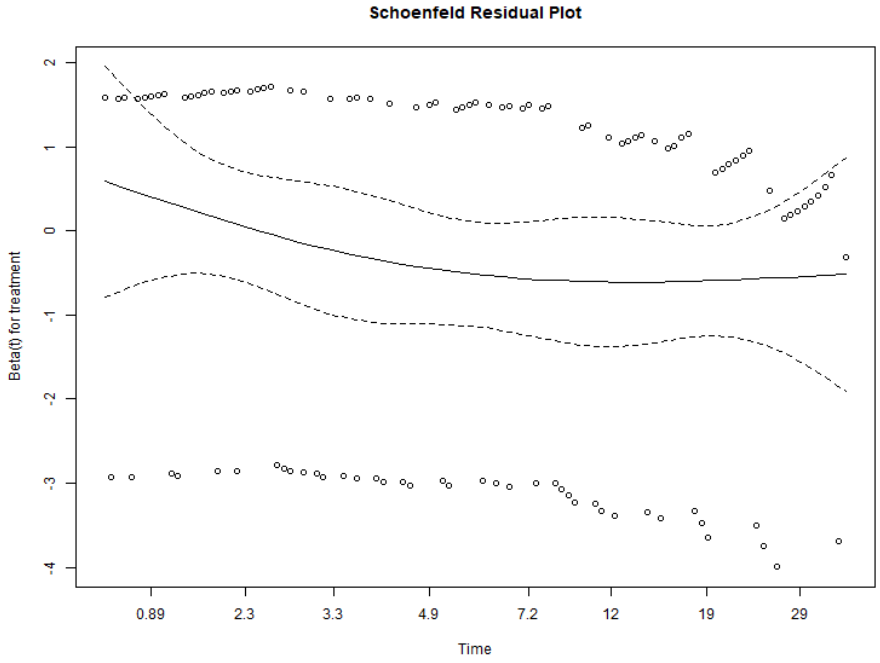


Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

Figure 30: Log-cumulative hazards plot for nivolumab and IC time to treatment discontinuation (PD-L1 <1%)

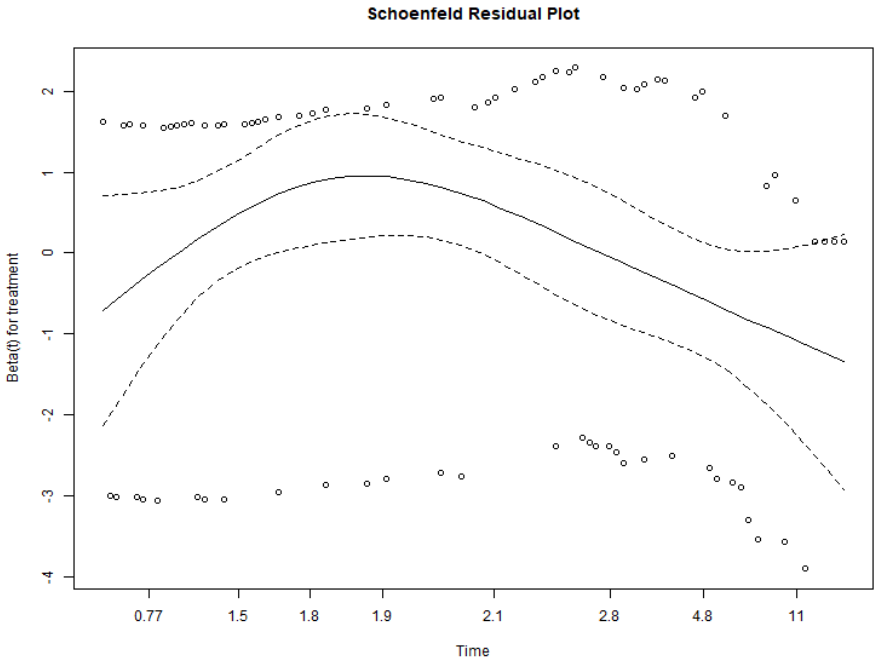
Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

Figure 31: Schoenfeld residual plot for nivolumab and IC overall survival (PD-L1 <1%)



Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

Figure 32: Schoenfeld residual plot for nivolumab and IC progression-free survival (PD-L1 <1%)



Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

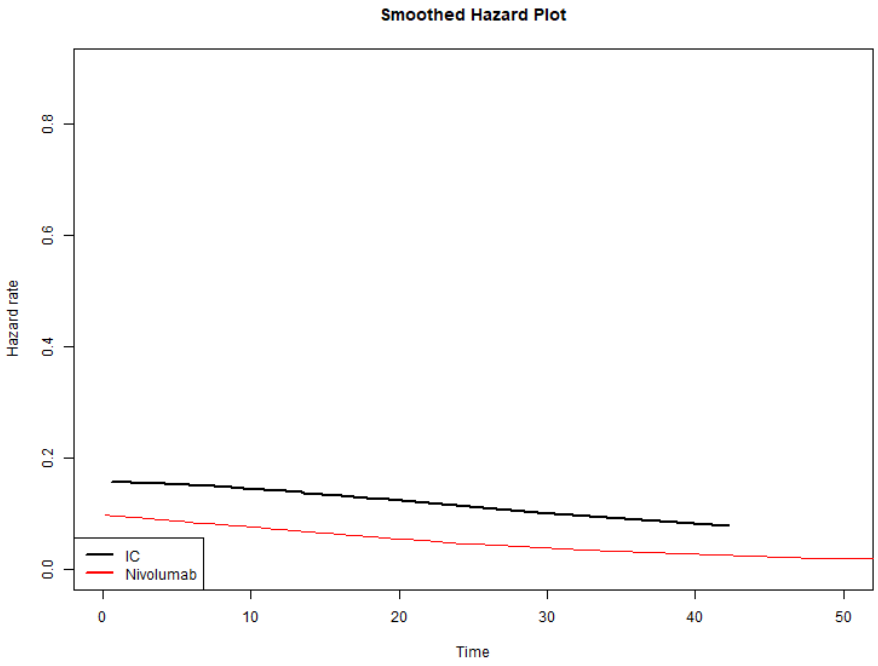
Figure 33: Schoenfeld residual plot for nivolumab and IC time to treatment discontinuation (PD-L1 <1%)

[redacted]

Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

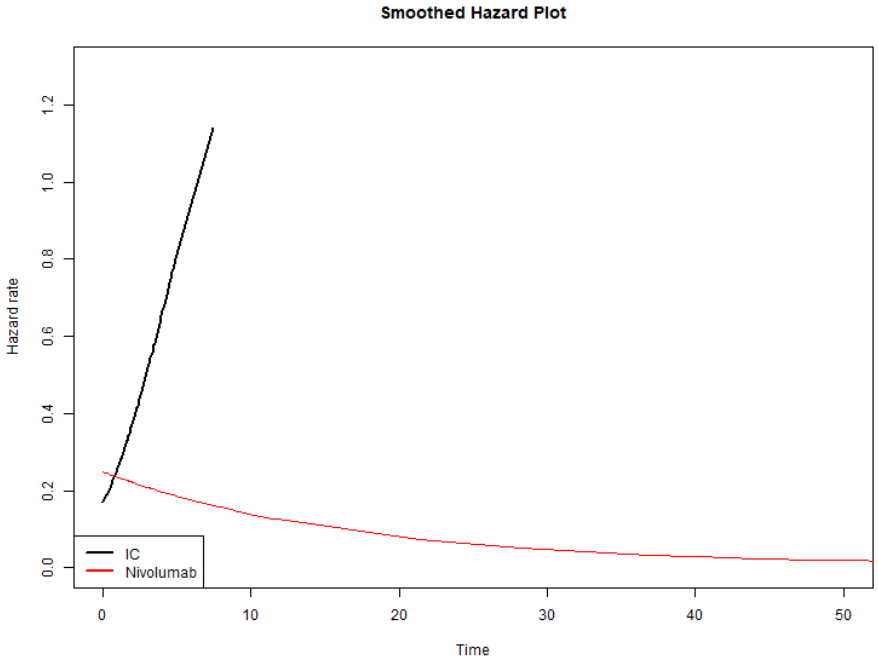
PD-L1 ≥1%

Figure 34: Smoothed hazards plot for nivolumab and IC overall survival (PD-L1 ≥1%)



Abbreviations: IC: investigator's choice.

Figure 35: Smoothed hazards plot for nivolumab and IC progression-free survival (PD-L1 ≥1%)

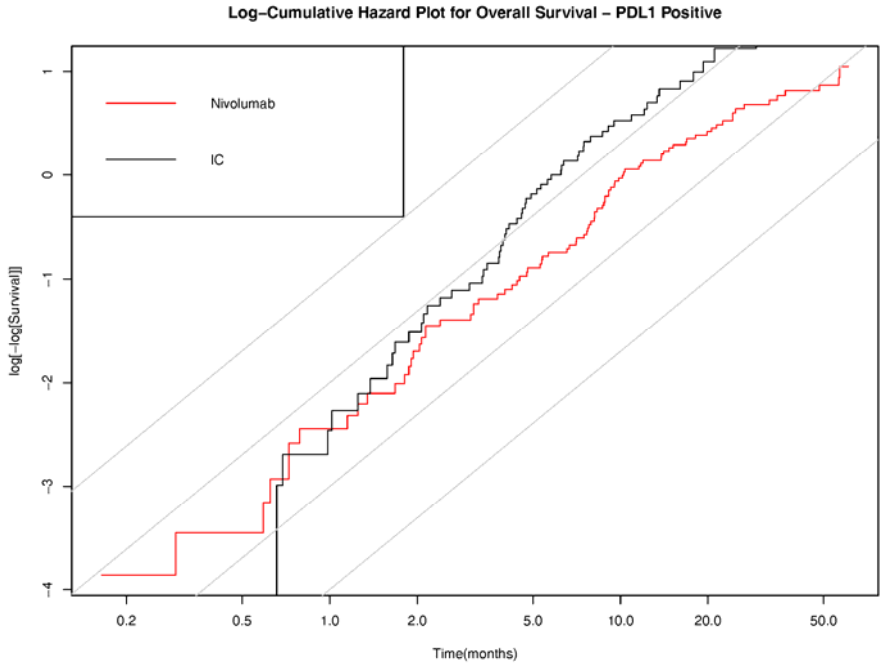


Abbreviations: IC: investigator's choice.

Figure 36: Smoothed hazards plot for nivolumab and IC time to treatment discontinuation (PD-L1 ≥1%)

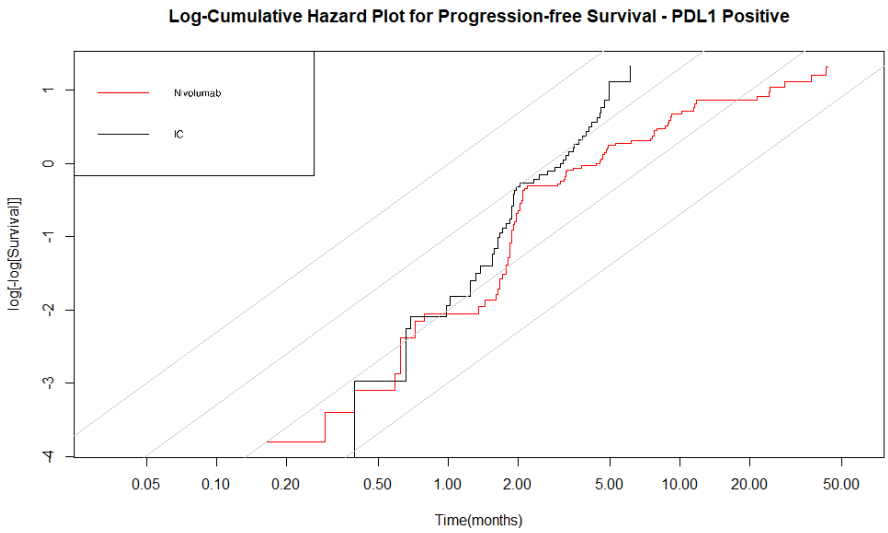
Abbreviations: IC: investigator's choice.

Figure 37: Log-cumulative hazards plot for nivolumab and IC overall survival (PD-L1 ≥1%)



Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

Figure 38: Log-cumulative hazards plot for nivolumab and IC progression-free survival (PD-L1 ≥1%)



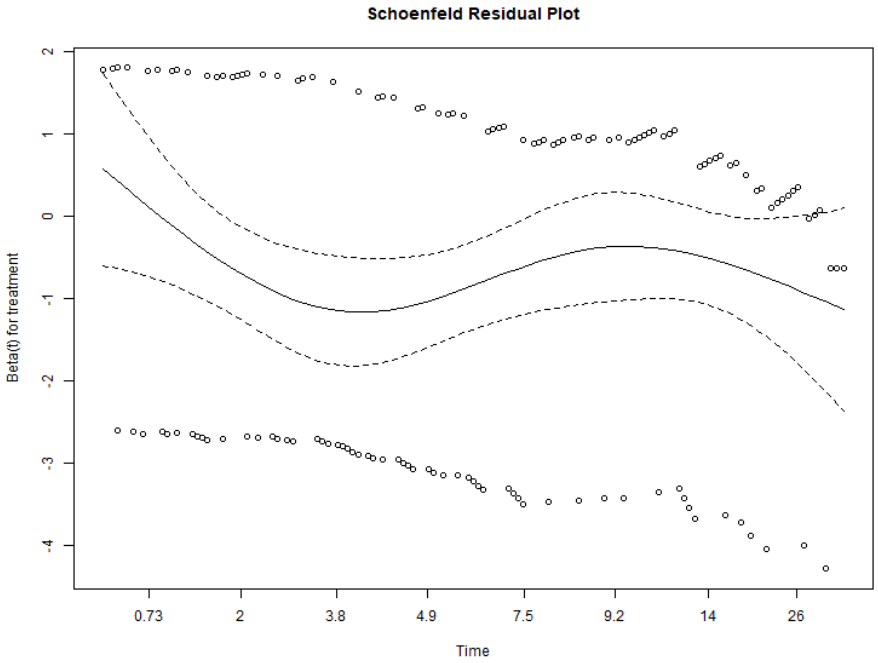
Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

Figure 39: Log-cumulative hazards plot for nivolumab and IC time to treatment discontinuation (PD-L1 ≥1%)

[redacted]

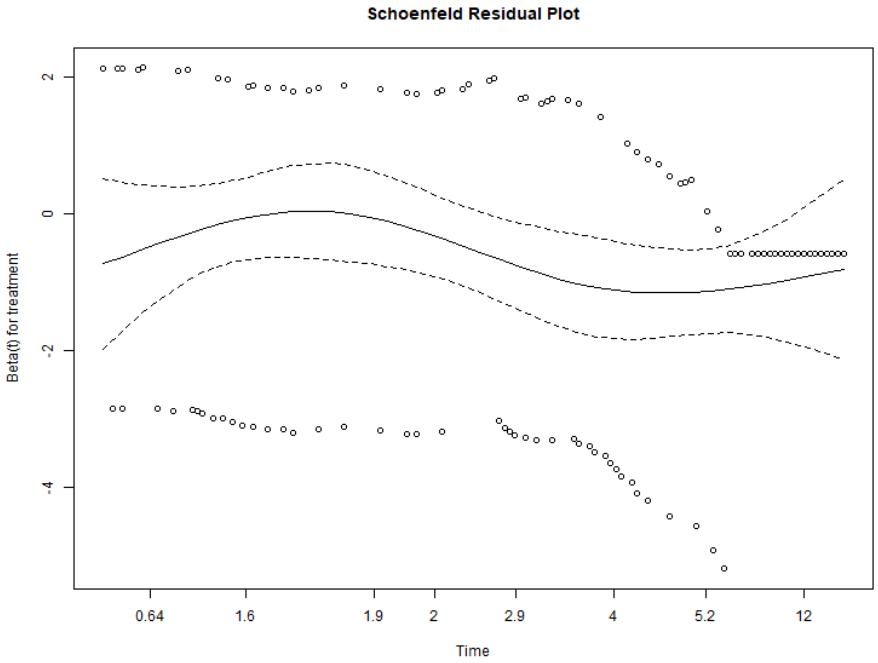
Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

Figure 40: Schoenfeld residual plot for nivolumab and IC overall survival (PD-L1 ≥1%)



Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

Figure 41: Schoenfeld residual plot for nivolumab and IC progression-free survival (PD-L1 ≥1%)



Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

Figure 42: Schoenfeld residual plot for nivolumab and IC time to treatment discontinuation (PD-L1 ≥1%)

Abbreviations: IC: investigator's choice; PD-L1: programmed death ligand 1.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (CDF Review of TA490) [ID1585]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Head and Neck Cancer UK (HANCUK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Registered Charity to act as an advocate and to assist patients to make informed decisions about their care and treatment; Raise awareness of all aspects of head and neck cancer, particularly its symptoms, diagnosis and treatment; Provide information, advice and support. Funded by grants and donations Not a membership organisation. There are 5 Trustees with contact with scores of patients
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Series of meetings, courses and seminars held throughout England and Scotland
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Head and Neck Cancer relates to a number of different cancers affecting the Head and Neck. Typically, patients experience a variety of difficulties depending upon the source of the cancer and the treatment. These include changes to appearance with the effects on well -being; depression, loss of feeling, inability to eat normally, loss of taste, discomfort, dry mouth etc. ,Additionally, concerns surrounding the impact of treatment options for recurrent or metastatic disease will be uppermost in patients thoughts. Carers have to deal with the practicalities of dealing with practical and psychological issues

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The treatments offered vary according to the patients location. Some hospitals offer treatment which is not available in other areas, particularly rural areas. Care and support is patchy
8. Is there an unmet need for patients with this condition?	There is room for improvement in many aspects of treatment of Head & Neck Cancer. Techniques continue to evolve but many leave patients with life changing conditions. We have been unable to find patients familiar with the comparators within the timescale.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We have been unable to find a patient who has experienced the technology/drug
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We have been unable to find a patient who has experienced the technology/drug

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not known at this stage
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The physical and psychological health of the patient must be paramount
- The impact on daily living must be a major consideration
- It is important that there are more options for treatment
- Patients must be fully consulted and appraised of any new drug/technology offered; together with any side effects

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Patient organisation submission

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You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	The Swallows Head & Neck Cancer Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a charity supporting Head & Neck Cancer patients and caregivers on a 24/7 basis, plus creating awareness of this cancer and drive campaigns for early diagnoses. Over 7000 members We are funded via our charity shop, grants and fundraising
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	None

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	Talking to our network of patients and caregivers
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Fear of cancer returning is a common factor with the majority of Head & Neck cancer patients, so when it actually happens the diagnoses is the worse news you can get It can affect the mental state, attitude, understanding of the recurrence. You then need to deal with the uncertainty of the future and what treatment is or not available. Recurrence of the cancer to many people in HnC means either palliative or trying new drugs to deal with the diagnoses but are not prepared for the journey ahead – hanging on to life is important but patients still say 'I wish I hadn't held on with the QoL I am left with'

	Living with the Outcomes of cancer is sometimes harder than the actual treatment, dealing with the many side effects such as: • Dry Mouth • Fatigue • Fear of returning cancer • Disfigurement • Social inclusion • Returning to work • Restricted Mobility • Impact on Quality of Life (self-care, dressing, washing, decision making, eating, drinking, and communicating • Depression and dealing with suicide thoughts 'Why me' 'Can't go on like this'
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Very good but always room to improve such as, Quality of Life, Survivorship, Side Effects, Access to New Drugs, Information overload, Outcomes, Experience during and post treatment. Side effects of most drugs and treatment for HnC has an impact on the life post treatment. Side effects are listed in section 6
8. Is there an unmet need for patients with this condition?	Yes, Patient to Patient & Caregiver to Caregiver support for the help/support in the unmet need of dealing with the many side effects of the treatment, during and post treatment. Once in the community they are on their own and need to deal with issues as they arrive.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients who have been on Nivolumab have stated that the treatment was of benefit but would have liked more understanding of the outcomes and impact on QoL
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Impact on QoL in years gained
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The challenges in managing this condition when people with the condition also have other medical conditions? • Managing the treatment and condition at home • Caregiver needing to understand more about the treatment & side effects to look for • Current medicine and treatment and the impact on this with the new drug Groups of people with the condition who might benefit more from this treatment than others? • Younger age patient, longer life and mayay fitter to deal with the treatment Groups of people with the condition who might benefit less from this treatment than others? • Older age group as they may suffer from side effects and the ability to deal with these, benefit over results.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Equality issues are important; Groups of people with the condition may have issues with… • Religious concerns • Cultuture concerns • Language barriers • Age to understand the diagnoses and treatment • Who will ngive concent in the above groups, so the caregiver becomes more important Groups of people with the condition who have difficulties using the currently available treatments? • As above list
Other issues	
13. Are there any other issues that you would like the committee to consider?	I would like the committee to always understand what impact this will have on Quality of Life and what support is available in the community setting
Key messages	
1. I would like the committee to always understand what impact this will have on Quality of Life and what support is available in the community setting 2. Equality issues are important	

3. Patients who have been on Nivolumab have stated that the treatment was of benefit but would have liked more understanding of the outcomes and impact on QoL
4. Living with the Outcomes of cancer is sometimes harder than the actual treatment, dealing with the many side effects

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (CDF Review of TA490) [ID1585]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Andrew Sykes**
2. Name of organisation	**Christie Hospital NHS Foundation Trust**

3. Job title or position	**Consultant Clinical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop progression of disease, improve overall survival and improve quality of life
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Nivolumab doubles survival at 12 months and more than doubles survival at 24 months. I consider this to be a very significant benefit.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is definitely an unmet need. Nivolumab is the first and only treatment that improves survival after the failure of palliative platinum base chemotherapy. It not only improves survival, but it also improves quality of life.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	After platinum failure selected patients are offered taxane chemotherapy. It is toxic however and only benefits a small qroup of patients who have symptomatic progression that responds to taxanes. In most cases side effects outweigh any benefit.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines recommend the use of first line palliative platinum based chemotherapy. On progression it is recognised that conventional chemotherapy has little to offer most patients and so those that are offered taxanes are a very select group.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined. To a large degree this is due to the limited number of effective treatment options. Nivoloumab is now recognised as the treatment of choice after platinum failure.
• What impact would the technology have on the current pathway of care?	It gives us an effective, well tolerated treatment that improves survival and quality of life for patients with inoperable/metastatic head and neck SCC. The only treatment to do so after platinum failure.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	We will continue to use it in the way that it is being used through bluteq. Standard NHS practice is to offer it to PS 0-1 patients after platinum failure.

• How does healthcare resource use differ between the technology and current care?	Novolumab is already being used via bluteq. Without Nivolumab we would be limited to treating a few selected patients with taxane chemotherapy which is of limited benefit.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist tertiary setting. Nivolumab should only be prescribed by trained oncologist experienced in the use of immunotherapy
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None as this treatment has been used for the last 2 years and clinics are already established.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	yes
• Do you expect the	Yes

technology to increase health-related quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The bluteq application is already quite specific that it should be for patients PS 0-1 who have progressed within 6 months of platinum chemotherapy.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Nivolumab is much easier to use than taxane chemotherapy. The side effect profile for most patients is significantly less toxic

or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The stopping rules are already established on the bluteq application process (progression, unmanageable toxicity or 2 years of treatment)
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes, It significantly improves survival and quality of life when compared to standard taxane chemotherapy

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, it is the first and only treatment to demonstrate a survival benefit after platinum failure.
• Does the use of the technology address any particular unmet need of the patient population?	It improves both survival and quality of life.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In most cases toxicity is minimal and manageable. Rarely patients can experience potentially severe auto-immune side effects. Compared the taxane chemotherapy though Nivolumab is very well tolerated.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.

• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival Yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. In fact the benefits observed in the trials can be replicated in the more diverse population seen in clinics. We have audited the results from over 100 patients and are confident that Nivolumab is effective
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Our own audit of patients treated across 3 large hospitals (Christie, Leeds and Sheffield). This demonstrated results comparable with the Checkmate 141 trial
21. How do data on real-world experience compare with the	Our own audit of patients treated across 3 large hospitals (Christie, Leeds and Sheffield). This demonstrated results comparable with the Checkmate 141 trial. Treatment is well tolerated in the real-

trial data?	world
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	NA
Topic-specific questions	
23. Is a 2-year stopping rule for nivolumab appropriate?	I have some concerns about this. We are only just coming up to the 2 year point for patients who have responded well. I do not know what will happen when we stop Nivolumab and fear that if patients' disease progresses we will be very limited in what we can offer them.
24. Would you expect the benefit of treatment with nivolumab to continue after treatment has been stopped,	I do not know

and if so, for how long?	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Nivolumab is the only effective treatment after platinum failureNivolumab improves overall survival (double at 12 months and more than doubled at 24 months)
- Nivolumab improves quality of life
- Nivolumab is well tolerated with a manageable side effect profile
- Our own data shows that Nivolumab is as effective in the real world as in the clinical trials

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Christopher Curtis**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ✓ other (please specify):
3. Name of your nominating organisation	The Swallows Head & Neck Cancer Charity
4. Did your nominating organisation submit a submission?	✓ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	✓ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	✓ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ✓ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Fear of cancer returning is a common factor with the majority of Head & Neck cancer patients, so when it actually happens the diagnoses is the worse news you can get It can affect the mental state, attitude, understanding of the recurrence. You then need to deal with the uncertainty of the future and what treatment is or not available. Recurrence of the cancer to many people in HnC means either palliative or trying new drugs to deal with the diagnoses but are not prepared for the journey ahead – hanging on to life is important but patients still say 'I wish I hadn't held on with the QoL I am left with' Living with the Outcomes of cancer is sometimes harder than the actual treatment, dealing with the many side effects such as:

	• Dry Mouth • Fatigue • Fear of returning cancer • Disfigurement • Social inclusion • Returning to work • Restricted Mobility • Impact on Quality of Life (self-care, dressing, washing, decision making, eating, drinking, and communicating Depression and dealing with suicide thoughts 'Why me' 'Can't go on like this' Caregivers are on the same journey but on different tracks – they need to pick up all the issues and care for the patient with NO training, also no one to turn to for help or support
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Caregivers think treatment is very good, but they feel like the 4th hidden person in the room with no guidance or support. Health professionals do not look at the caregiver it s always aimed at the patient
10. Is there an unmet need for patients with this condition?	Nivolumab the improvement is not as big as was hoped and in some cases no improvement in QoL Support and the ability to live longer without impacting Quality of Life and less side effects or better management of the side effects.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Simple it gives the patient an opportunity of a Longer life
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Impact on the QoL and outcomes of the treatment
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The challenges in managing this condition when people with the condition also have other medical conditions? • Managing the treatment and condition at home • Caregiver needing to understand more about the treatment & side effects to look for • Current medicine and treatment and the impact on this with the new drug Groups of people with the condition who might benefit more from this treatment than others? • Younger age patient, longer life and mayay fitter to deal with the treatment Groups of people with the condition who might benefit less from this treatment than others? • Older age group as they may suffer from side effects and the ability to deal with these, benefit over results.
Equality	
14. Are there any potential equality issues that should be	Equality issues are important;

taken into account when considering this condition and the technology?	Groups of people with the condition may have issues with… • Religious concerns • Cultuture concerns • Language barriers • Age to understand the diagnoses and treatment • Who will ngive concent in the above groups, so the caregiver becomes more important Groups of people with the condition who have difficulties using the currently available treatments? • As above list
Other issues	
15. Are there any other issues that you would like the committee to consider?	I would like the committee to always understand what impact this will have on Quality of Life and what support is available in the community setting
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: 1. I would like the committee to always understand what impact this will have on Quality of Life and what support is available in the community setting 2. Equality issues are important 3. Patients who have been on Nivolumab have stated that the treatment was of benefit but would have liked more understanding of the outcomes and impact on QoL 4. Living with the Outcomes of cancer is sometimes harder than the actual treatment, dealing with the many side effects	

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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: CDF review of TA490

Produced by Kleijnen Systematic Reviews Ltd. (KSR) in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)

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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

AE	adverse event
AIC	Akaike information criterion
ALK	anaplastic lymphoma kinase
ASBI	Average Symptom Burden Index
AUC	area under the curve
BIC	Bayesian information criterion
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BOR	best objective response
BRAF	B-Raf proto-oncogene
BSC	best supportive care
BTLA	B- and T-lymphocyte attenuator
CD27	cluster of differentiation 27
CD28	cluster of differentiation 28
CD137	cluster of differentiation 137
CDF	Cancer Drugs Fund
chemo	chemotherapy
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
COMP	comparator
CR	complete response
CSR	clinical study report
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte antigen-4
DMC	Data Monitoring Committee
DOR	duration of response
DoT	duration of treatment
DSA	deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	electronic market information tool
EQ-VAS	EQ-5D Visual Analogue Scale
ER	endoplasmic reticulum
ERG	Evidence Review Group
EU	European Union
GCP	good clinical practice
GITR	glucocorticoid-induced tumour necrosis factor receptor
GP	general practitioner
HIV	human immunodeficiency virus
HR	hazard ratio
HRG	Healthcare Resource Groups
HRQoL	health-related quality of life
HTA	health technology assessment
HVEM	herpes virus entry mediator
IC	investigator's choice
ICER	incremental cost-effectiveness ratio
IgG4	immunoglobulin G4
IMAE	immune-mediated adverse event
INT	intervention

IO	immuno-oncology
IO-IO	immuno-oncology–immuno-oncology combination therapy
ipi	ipilimumab
IRRC	independent radiology review committee
IV	intravenous/intravenously
IVRS	interactive voice response system
LAG3	lymphocyte-activation gene 3
LCSS	Lung Cancer Symptom Scale
LS	least squares
LY	life-year
LYG	life-year gained
MHC	major histocompatibility complex
MID	minimally important difference
MRI	magnetic resonance imaging
mut/Mb	mutations per megabase
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nivo	nivolumab
NR	not reached
NSCLC	non-small cell lung cancer
NSQ	non-squamous
ORR	objective response rate
OS	overall survival
OX40	tumour necrosis factor receptor superfamily, member 4
PAS	patient access scheme
PD	progressed disease
PD-1	programmed death-1
PDC	platinum doublet chemotherapy
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PF	progression-free
PFS	progression-free survival
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q12W	every 12 weeks
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QALY	quality-adjusted life-year
RANK-L	receptor activator of nuclear factor kappa-B ligand
RCT	randomised controlled trial
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
ROC	receiver operating characteristic
ROS1	ROS proto-oncogene 1
SACT	Systemic Anti-Cancer Therapy
SAE	serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
SLR	systematic literature review
SmPC	summary of product characteristics
SQ	squamous

STA	single technology appraisal
TAP	transporter associated with antigen processing
TCR	T-cell receptor
TIM3	T-cell immunoglobulin and mucin-domain containing-3
TMB	tumour mutational burden
ToE	terms of engagement
TPS	tumour proportion score
TRAE	treatment-related adverse event
TTD	time to treatment discontinuation
TTR	time to response
UK	United Kingdom
US	United States
VAS	visual analogue scale
VISTA	V-domain immunoglobulin suppressor of T-cell activation
WTP	willingness to pay

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1. EXECUTIVE SUMMARY

1.1 Critique of the adherence to committees preferred assumptions from the Terms of Engagement (ToE) in the company's submission

The following is a list of the key committee assumptions (preferences) according to the ToE for the Cancer Drugs Fund (CDF) review, each one followed by a statement as to the Evidence Review Group's (ERG's) finding of the extent to which the company submission (CS) has adhered to the committee preferences (See Section 2.2 for more details).

Assumption 0: Nivolumab administered according to a weight base dose (3 mg/kg every two weeks). This was not specified in the ToE, but it might be regarded a tacit assumption. Since the original submission for TA490, on 28 April 2017 the licensed dose of nivolumab has been updated to a flat dose of 240 mg every two weeks (Q2W). The ERG questions the validity of the conclusion by the company that there will be no clinically meaningful difference between weight-based and the specific flat dose of 240 mg in terms of effectiveness and safety given that many patients will have to either increase or decrease dosage.

Assumption 1: Population: adults with recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN) that progressed within six months of platinum-based therapy, in either the early or locally advanced disease stage. The ERG notes that there is an apparent discrepancy in that the eligibility criteria for CheckMate 141 include progression at the metastatic or recurrent disease stage. However, there is correspondence between CheckMate 141 and the Systemic Anti-Cancer Therapy (SACT) dataset and the ToE also stated that the CheckMate 141 results are relevant to the population of interest and therefore then this could be considered as tantamount to adherence to the committee's preferred assumption.

Assumption 2: Docetaxel is the comparator of interest. The ERG notes that there appears to be incomplete adherence in that, although it is a comparator in the cost effectiveness analysis, the clinical effectiveness data used to inform this analysis and the clinical effectiveness evidence presented were based on a comparison of nivolumab to investigator choice (IC), i.e. using the all-randomised (full intention to treat) data. Using the all-randomised data, including that from the whole IC arm implies equivalence between docetaxel and methotrexate, which the ToE explicitly rejects. The ERG would therefore argue that the best source of evidence for a comparison with docetaxel should be the subgroup of those chosen to receive docetaxel according to IC (docetaxel subgroup).

Assumption 3: CheckMate 141 data to be used. The ERG can confirm that this assumption was adhered to in the CS, notwithstanding the omission of the docetaxel subgroup.

Assumption 4: Overall survival from CheckMate 141 data updated. The ERG can confirm that this assumption was adhered to in the CS.

Assumption 5: Analysis of the effect of PD L1 expression on updated OS. The ERG can confirm that this assumption was adhered to in the CS.

Assumption 6: No change in model structure. The ERG can confirm that the model structure was unchanged.

Assumption 7: Piecewise model used for extrapolation of survival: timepoint to extrapolate and distribution to be explored. The ERG can confirm that piecewise models were indeed used to extrapolate survival while using alternative cut-off points and two different distributions.

Assumption 8: Continued treatment benefit to be reviewed in light of any new evidence. The ERG notes that the company argued that in light of the new evidence, the assumption of continued treatment benefit (i.e. no treatment waning) was plausible. The ERG, however, preferred to incorporate treatment waning of the nivolumab OS benefit after year 5.

Assumption 9: Quality-of-life benefit of nivolumab cannot be assumed to remain constant. Exploration of the most appropriate utility values should be reviewed in light of any new evidence. The ERG notes that this was only done partly as health state utility values are not updated and it is questionable whether the company's approach to incorporate utility benefit over time appropriately addresses the concerns raised in the ToE.

Assumption 10: The ToE stipulated that the committee considered analyses without a stopping rule are more appropriate for decision-making. However, the appropriateness of a two-years stopping rule should be reviewed in light of any new evidence. The ERG notes that the company stated that based on the time to treatment discontinuation (TTD) extrapolation used in its base-case, [redacted], and a two-year stopping rule has been shown to be clinically plausible during the CDF data collection period. The ERG preferred to exclude the two-year stopping rule, consistent with committee preferences as reported in the ToE.

Assumption 11: ERG amendments will be included (adding the cost and disutility for pneumonitis and using treatment-independent proportions for subsequent treatment). The ERG can confirm that these amendments were included.

1.2 Summary of key issues in the clinical effectiveness evidence

1) Update of CheckMate 141 overall survival (OS) data, according to the ToE: The ERG can confirm that this has been done with the latest data cut being 15 October 2019, i.e. four years follow-up. The results show that the survival advantage of nivolumab over IC was maintained in terms of hazard ratio (HR) and median survival and continued through 36 months and at 48 months. Also, the company provided the up to date data from CheckMate 141 on progression-free survival (PFS) and the ERG can confirm that there is no fundamental change in interpretation: the advantage of nivolumab versus IC in terms of HR and the small advantage of IC versus nivolumab in terms of median survival, were maintained, although neither were statistically significant. Although the ToE did not specify an update in terms of safety, it appears from the company response to clarification, that little has changed in both the number and percentage of AEs between TA490 and the CDF review, which leads to the same conclusion as found by the ERG in TA490, i.e. 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). Given that the committee concluded that the comparator should be docetaxel, the ERG considers that the most appropriate evidence of effectiveness and safety versus docetaxel is that from the docetaxel subgroup, which the company did not provide in either the CS or in response to the clarification letter. The ERG considers that this is a major source of uncertainty that can be reduced by the company.

2) SACT dataset to assess the generalisability of CheckMate 141, according to the ToE: A comparison reveals that UK patients might be slightly older and a small number will have a worse performance status than the patients in the all-randomised population of the CheckMate 141 trial, which might suggest that UK patients do slightly worse than patients in the CheckMate 141 trial. However, although patients in the SACT dataset had a numerically lower median survival than those in the nivolumab arm of Check Mate 141, it is important to remember that this was based on a much shorter median follow-

up and the 95% CIs overlapped. Also, one-year survival was very similar. As mentioned with regards to the comparison between nivolumab and docetaxel, it could be argued that the nivolumab arm of the docetaxel subgroup of CheckMate 141 should be used to compare with the SACT dataset. On the other hand, the all-randomised population might be closer to those patients who would be treated with nivolumab in UK clinical practice. This was the judgment of the committee, who concluded that the CheckMate 141 results (implying the all-randomised population) are relevant to the population of interest, i.e. adults with recurrent or metastatic SCCHN that progressed within six months of platinum-based therapy, in either the early or locally advanced disease stage. Although there is a discrepancy between descriptions of eligibility criteria, those for the SACT dataset could also be regarded as essentially the same as those for CheckMate 141. However, clearly not everyone in CheckMate 141 was found to be eligible for docetaxel according to the IC design. In particular, some were chosen to receive methotrexate, which in the ToE states that it is only for patients who are not fit to have a taxane. The implication of this should be that the population specified for this CDF review and in the SACT dataset should not be aligned with the all-randomised population, but should at least exclude those who would be ineligible for docetaxel. This apparent mismatch between the population and the comparator specified in the ToE does produce some uncertainty in the generalisability of the CheckMate 141, which might be reduced by a comparison of the baseline characteristics and OS in the nivolumab arm of the docetaxel subgroup and the SACT dataset.

3) In terms of PD-L1 status, nivolumab showed an advantage in comparison to IC for both groups, but it was larger for those with PD-L1 ≥ 1% and only statistically significant for this subgroup. However, there was no significant evidence of a treatment and subgroup interaction (p=0.239) and these results should be considered with caution due to the reduced sample sizes and wider confidence intervals. For PFS, HRs were not provided for the PD-L1 subgroups, but the median PFS estimates indicate that there were no significant differences in PFS between nivolumab and IC in patients with PD-L1 <1% or those with PD-L1 ≥ 1%. There was also evidence of only a weak interaction effect. [redacted]

1.3 Summary of the key issues in the cost effectiveness evidence

The company base-case incremental cost effectiveness ratio (ICER) (probabilistic) of nivolumab (with patient access scheme (PAS)) compared with docetaxel was £36,255 per quality-adjusted life-year (QALY) gained. The ERG has incorporated various adjustments to the company base-case. The ERG base-case resulted in an ICER range (probabilistic) of £54,348 to £61,293 per QALY gained for nivolumab (with PAS) versus docetaxel. 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 states;
3) including treatment waning of nivolumab OS benefit after year 5 and;
4) excluding the two-year stopping rule.

Additionally, the company explored using SACT data to estimate TTD (i.e. nivolumab treatment duration) in scenario analyses. Compared with the CheckMate 141 trial, the SACT data provides real-world data that might better reflect UK clinical practice. The higher TTD observed in the SACT data resulted in a substantially increased ICER (+£14,198 compared to the CS base-case) highlighting the importance of the TTD assumptions in the model.

The equivalence assumptions between docetaxel and methotrexate as well as between the nivolumab flat dose and weight-based nivolumab can be questioned. Unfortunately, the company did not provide analyses based on the docetaxel subgroup (requested during the clarification phase), nor evidence to support the equivalence assumption between the flat dose and the weight-based dose of nivolumab. An additional area of uncertainty is the extrapolation of the nivolumab quality-of-life benefit over time. Although the company implemented utility decrements related to the time to death, the ERG believes that the committee's concern (i.e. emphasising that quality-of-life benefit cannot be assumed to remain constant over time) is not appropriately addressed. Therefore, the ERG base-case is presented as a range conditional on treatment dependent and treatment independent utilities to address the uncertainty related to the nivolumab utility benefit over time.

The subgroup analyses (based on PD-L1 status) performed by the ERG resulted in ICERs that ranged between £53,152 and £62,895 per QALY gained. It should however be noted that these subgroup analyses did not incorporate any additional costs related to PD-L1, which would be required if PD-L1 testing is not part of UK clinical practice.

In conclusion, the ERG base-case ICERs are estimated to be in the range between £54,348 and £61,293 per QALY gained, reflecting the uncertainty related to nivolumab quality-of-life benefits over time. Uncertainty that was not captured in this range included the equivalence assumptions between docetaxel and methotrexate as well as between the nivolumab flat dose and weight-based nivolumab. Additionally, if the nivolumab treatment duration from the SACT is believed to better reflect UK clinical practice (than TTD from CheckMate 141), this would substantially increase the estimated ICERs.

1.4 Summary of ERG's preferred assumptions and resulting ICER

Table 1.1: ERG analyses (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
Company base-case					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.35	[redacted]	[redacted]	£37,236
1 Company base-case + OS treatment waning[a]					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.35	[redacted]	[redacted]	£45,017
2 Company base-case + generalised gamma model for estimating TTD					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,505	0.35	[redacted]	[redacted]	£39,959
3 Company base-case + treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.38	[redacted]	[redacted]	£41,418
4 Company base-case					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
+ excluding the 2-year stopping rule					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.35	[redacted]	[redacted]	£49,018
5 Company base-case + correcting error related to implementation of docetaxel dose intensity					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,561	0.35	[redacted]	[redacted]	£37,254
6 ERG base-case 1 Company base-case + OS treatment waning + generalised gamma model for estimating TTD + excluding the 2-year stopping rule					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.35	[redacted]	[redacted]	£53,485
7 ERG base-case 2 Company base-case + OS treatment waning + generalised gamma model for estimating TTD + excluding the 2-year stopping rule + treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.38	[redacted]	[redacted]	£60,094

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation
[a]A minimum function was implemented to prevent that PFS would exceed OS (implemented in cells 'Nivolumab Traces'!G11:G370 and 'Docetaxel Traces'!G11:G370)
[b]The following cells were adjusted: Settings!J72:N72, 'Treatment Costs'!N24 and 'Docetaxel Traces'!AU11:AU369

Table 1.2: ERG base-case (probabilistic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility[a]					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,556	0.36	[redacted]	[redacted]	£54,348
7 ERG base-case 2 - treatment independent utility[a]					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,511	0.38	[redacted]	[redacted]	£61,293

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation
[a]The PSA produced 1 to 2 errors (#VALUE), these simulations were ignored to calculate the probabilistic means.

Table 1.3: ERG base-case; PD-L1 <1% subgroup (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,048	0.41	[redacted]	[redacted]	£53,152
7 ERG base-case 2 - treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,048	0.43	[redacted]	[redacted]	£62,895
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation					

Table 1.4: ERG base case; PD-L1 ≥1% subgroup (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£9,981	0.29	[redacted]	[redacted]	£54,362
7 ERG base-case 2 - treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£9,981	0.31	[redacted]	[redacted]	£58,926
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation					

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Table 1.5: ERG scenario (deterministic), nivolumab with PAS for all-randomised population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility + excluding the estimated utility decrements related to time before death					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.36	[redacted]	[redacted]	£50,140
7 ERG base-case 2 - treatment independent utility + excluding the estimated utility decrements related to time before death					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.40	[redacted]	[redacted]	£60,264
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation					

2. INTRODUCTION AND BACKGROUND

2.1 Background

The ToE for the CDF review states the following:[1] "Nivolumab is recommended for use within the Cancer Drugs Fund as an option for treating squamous cell carcinoma of the head and neck (SCCHN) in adults whose disease has progressed on platinum-based chemotherapy, only if:

- the disease has progressed within 6 months of having chemotherapy
- nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression and
- the conditions in the managed access agreement are followed."

The committee concluded that based on a PAS of [redacted] and its preferred assumptions the most plausible ICER would fall between £45,000 and £73,600 per QALY (dependent on the time point for extrapolation and treatment-dependent/independent utility values) for the full trial population, irrespective of PD-L1 expression.

Nivolumab was accepted in the CDF on the basis of two main conditions, which formed the managed access agreement:

1) A further discount, i.e. [redacted] commercial access agreement, which implied an ICER of £30,377 and £49,408 per QALY gained depending on the time point used for extrapolation and assuming a 2-year stopping rule.

2) A data collection agreement, reported as follows:[1]

- "The pivotal clinical-effectiveness evidence for nivolumab compared with investigator-choice was taken from the CheckMate 141 trial. This trial is the primary source for data collection under the managed access agreement. 4-year follow-up data would be undertaken based on the trial protocol including the reporting of OS, treatment duration and sub-group analysis by PD-L1 expression level. The company will provide updated evidence on the CheckMate 141 trial.
- Observational data will also be collected for nivolumab during the period of managed access via the systemic anti-cancer therapy (SACT) dataset to support the data collected in the clinical trial. SACT will collect data on OS, duration of therapy and PDL-1 expression. Public Health England will provide a summary of the observational data collected."

The index population is consistent with a subgroup of the licensed indication, i.e. "…recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) in adults progressing on or after platinum-based therapy".[2] The recommended dosage of nivolumab in this indication is 240 mg flat dose every two weeks. This is different to the weight-based dose of 3 mg/kg every two weeks that was recommended at the time of the original NICE appraisal for nivolumab in this indication.

2.2 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

Table 2.1 summarises the key committee assumptions (preferences) according to the ToE for CDF review.[1] It also summarises the extent to which the CS has adhered to the committee preferences.[2] In addition, the ToE state that the end-of-life criteria have been met.

ERG comments:

Assumption 0: Nivolumab dosing

There is a tacit assumption that was not specified in the ToE, which is the nature of the intervention, in particular the dosing regimen, no mention of which was made in the ToE.[1] Since the original submission for TA490, on 28 April 2017 the licensed dose of nivolumab was updated to a flat dose of 240 mg every two weeks (Q2W), rather than the weight-based dose used in the CheckMate 141 trial (3 mg/kg every two weeks).[2]

The company in their submission state that *"Nivolumab flat-dosing regimens are supported by clinical safety data and population pharmacokinetic modelling across many indications, which demonstrated that distributions of nivolumab exposures after 3 mg/kg Q2W and 240 mg Q2W were similar and below the exposures observed with 10 mg/kg Q2W. No clinically meaningful relationship between body weight or nivolumab exposure or nivolumab exposure quartiles and frequency or severity of adverse events was observed. Based on consistent exposure-response relationships across indications, the benefit-risk profile of nivolumab 240 mg Q2W is likely to be similar to 3 mg/kg Q2W, therefore the clinical effectiveness of nivolumab that was demonstrated in CheckMate 141 (weight-based dose) is expected to be generalisable to the use of nivolumab in clinical practice (flat dose)."*(p.9)[2] However, no reference to any source of evidence was provided.

There is the suggestion of some evidence that might provide some support for the use of the flat dose of 240mg from the web-site of the European Medicines Agency (EMA), which states that the introduction of the new dosing regimens of 240 mg every two weeks was based on a "comparison of the exposure-response and safety of nivolumab 3 mg/kg Q2W, 240 mg Q2W in … squamous cell cancer of the head and neck…" (p.11)[3] The summary of product characteristics also states: "Based on modelling of dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between a nivolumab dose of 240 mg every 2 weeks or 3 mg/kg every 2 weeks." (p.26)[4]

The ERG therefore requested empirical evidence from the company with references to support the claim that there will be no meaningful difference in either effectiveness or AE risk between the two methods of dosing, i.e. weight-based and flat dose. However, in response to clarification, the company did not provide any further evidence beyond those produced by the EMA.[3-5] Therefore, the ERG still questions the validity of the conclusion that there will be no clinically meaningful difference between weight-based and the specific flat dose of 240mg in terms of effectiveness and safety given that many patients will have to either increase or decrease dosage.

Assumption 1: Trial population

The committee concluded that, although there are some differences between the trial population and the UK population, the CheckMate 141 results are relevant to the population of interest, i.e. adults with recurrent or metastatic SCCHN that progressed within six months of platinum-based therapy, in either the early or locally advanced disease stage.[1] However, as shown in Table 3.1, the actual CheckMate 141 trial eligibility criteria included the recurrent, or metastatic setting. The ERG notes that it is unclear what difference this might make to the outcomes. However, also shown in Table 3.1, the SACT dataset applied the same additional criteria and therefore one might reasonably conclude that, if the SACT dataset represents clinical practice then the index population should include these additional criteria and also that CheckMate 141 trial is not compromised by this discrepancy.

Assumption 2: Docetaxel comparator

In the ToE, the committee also concluded that the comparator should be docetaxel.[1] They also raised concerns about the generalisability of CheckMate 141 and that it should not be assumed that docetaxel was comparable to the other comparator, methotrexate because it is only for patients who are not fit to have a taxane. The ERG would like to point out that one would therefore expect that the actual population that should be eligible for nivolumab would be only those who might otherwise receive docetaxel. However, it is unclear how this population might be defined precisely, e.g. according to ECOG performance status. There is also no indication from the SACT dataset report that only those eligible for docetaxel were given nivolumab in the CDF. Therefore, it is unclear which of the CheckMate 141 populations would be most representative of UK clinical practice, the all-randomised or the subgroup of patients eligible for docetaxel (who would have been chosen to receive docetaxel according to IC), i.e. those patients who were randomised to docetaxel vs. those who would have received docetaxel according to IC, but who were randomised to nivolumab. The ERG will refer to this subgroup from this point onwards as the 'docetaxel subgroup'.

Nevertheless, in order to assess the comparability of the nivolumab baseline characteristics and outcomes to the SACT dataset (Sections 3.1 and 3.2), it is less clear whether the docetaxel subgroup should be chosen. On the one hand, this would be consistent with the comparator being treated with docetaxel. On the other hand, if the population of the SACT dataset is the same as the CheckMate 141 trial all-randomised population then to exclude patients in the cetuximab or methotrexate subgroups would exclude patients who are also eligible for nivolumab. Nevertheless, the ERG would argue that, on balance, the effectiveness of nivolumab vs. docetaxel should be estimated from the docetaxel subgroup. Although the company used docetaxel as a comparator in the cost effectiveness analysis, it was based on data from the all-randomised population.[2] Because of this, the ERG requested the company to perform analyses in the docetaxel subgroup. The company responded by stating firstly that there was insufficient time to perform these analyses.[5] The company also argued that it had been demonstrated in TA490 that the comparisons using the docetaxel subgroup would have minimal impact on the cost effectiveness results, although no summary measures of treatment effect (e.g. HRs) were presented at that time.[6] This also adds additional uncertainty to the estimated cost effectiveness. The company goes on to present four more arguments against the docetaxel subgroup analyses:

1) the trial was not powered for subgroup analysis by IC. The ERG recognise that this is true, but this is not a reason not to present the analyses, but instead a reason for caution in interpretation.
2) because the choice of intended IC therapy was made prior to randomisation, the analysis of outcomes by individual therapies in the IC arm breaks randomisation and is at risk of selection bias. However, it is precisely because the choice was made before randomisation that there is no selection bias: all patients chosen to have a specific IC were randomised to either that choice of IC or nivolumab.
3) data from the all-randomised IC arm, regardless of specific subgroup, i.e. the all-randomised data, were found in the FAD of TA490 to be appropriate for decision making and that the ToE stipulates no deviation from the committee's preferred assumptions. However, the list of assumptions in the ToE does not explicitly state that only the all-randomised data should be used. The ToE also states, unlike in the FAD, that the comparator should be docetaxel.
4) it would be wrong to focus only on docetaxel as a comparator given that patients not fit enough to take it would receive methotrexate. This is not a reason to not provide the docetaxel subgroup data for a comparison with docetaxel, but instead might be a reason to provide the methotrexate subgroup data for a comparison with methotrexate.

Assumptions 3 to 8 and 11

The ERG can confirm that these assumption were adhered to in the CS, notwithstanding the omission of the docetaxel subgroup and the change in dosing referred to above.

Assumptions 9 and 10

The extent of adherence to these assumptions is discussed in detail in Chapter 4.

Table 2.1: Preferred assumption from ToE

Assumption	Terms of Engagement	Addressed to by the company submission	Rationale if different	ERG comment
Assumption 1	Population: adults with recurrent or metastatic SCCHN that progressed within 6 months of platinum-based therapy, in either the early or locally advanced disease stage.	Incomplete: mismatch with CheckMate 141 trial.	None given.	Probably not a problem. See Chapter 2 for details.
Assumption 2	Docetaxel is the comparator of interest.	Incomplete: Docetaxel subgroup data not presented or used in the cost effectiveness analysis.	None given.	See Chapter 2 for details.
Assumption 3	CheckMate 141 data to be used.	Yes	Not applicable.	See Chapter 3 for details.
Assumption 4	Overall survival from CheckMate 141 data updated	Yes	Not applicable.	See Chapter 3 for details.
Assumption 5	Analysis of the effect of PD L1 expression on updated OS	Yes	Not applicable	See Chapter 3 for details.
Assumption 6	No change in model structure	Yes	Not applicable	See Chapter 4 for details.
Assumption 7	Piecewise model used for extrapolation of survival: timepoint to extrapolate and distribution to be explored.	Yes	Not applicable	See Chapter 4 for details.
Assumption 8	Continued treatment benefit to be reviewed in light of any new evidence.	Yes	Not applicable	See Chapter 4 for details.
Assumption 9	Quality-of-life benefit cannot be assumed to remain constant. Exploration of the most appropriate utility values should be reviewed in light of any new evidence.	Incomplete, health state utility values were not updated and the approach to incorporate utility benefit over time might be debatable.	Not applicable	See Chapter 4 for details.

Assumption	Terms of Engagement	Addressed to by the company submission	Rationale if different	ERG comment
Assumption 10	Appropriateness of a 2-years stopping rule should be reviewed in light of any new evidence.	Incomplete, inclusion of stopping rule might be debatable.	Not applicable	See Chapter 4 for details.
Assumption 11	ERG amendments will be included (adding the cost and disutility for pneumonitis and using treatment-independent proportions for subsequent treatment).	Yes	Not applicable	Not applicable

Source: Based on table of key committee assumptions as reported in the Terms of engagement for CDF review.[1] and the company submission[2]
ERG = evidence review group; CDF = cancer drugs fund

3. CLINICAL EFFECTIVENESS

3.1 Overview of the new clinical evidence

3.1.1 Sources of evidence

The clinical efficacy of nivolumab in the treatment of SCCHN has been investigated in one RCT, CheckMate 141.[2, 7, 8] CheckMate 141 is a phase III, multicentre, open-label, active-controlled randomised trial comparing the efficacy and safety of nivolumab with investigator's choice (IC), which included choice at the clinician's discretion of docetaxel, methotrexate or cetuximab. Its main methodological features are summarised in Table 3.1. The new evidence from this trial is from the latest data cut of the trial (four-year; 15 October 2019).

The other source is the SACT dataset.[9] This was specified in the ToE and created, at the behest of NHS England and NHS Improvement, by Public Health England (PHE), with the purpose of evaluating the real-world treatment effectiveness of nivolumab in the CDF population during the managed access period.[1] It provides evidence on treatment duration, OS and the reasons for stopping treatment (described as 'treatment outcomes') for all patients treated with nivolumab for the same population as in the CheckMate 141 trial.

ERG comment: The SACT dataset permits to some degree a test of the generalisability of the outcomes observed in the CheckMate 141 trial, at least in the nivolumab arm, to UK clinical practice. For this reason, throughout the following sections the ERG will compare these two data sources both to establish comparability of outcomes in terms of design and baseline characteristics and in terms of the outcomes, OS and TTD.

3.1.2 Patient characteristics in CheckMate 141 and SACT

As noted in the previous ERG report, baseline characteristics seemed to be comparable between the two treatment arms of CheckMate 141 (nivolumab and IC), although unsurprisingly, given the IC design, this is not the case between the various treatments (Table 3.2).[6] For example, the percentage of patients who have received at least three lines of therapy is higher for methotrexate and nivolumab than for docetaxel.

The company provided a summary and table comparing the baseline characteristics of the nivolumab arm of the CheckMate 141 trial and the SACT cohort reported by Public Health England. See Table 3.3. Limited information was available concerning the SACT cohort so comparisons can only be made on gender, age, ECOG performance status and PD-L1 scores. It can be seen in Table 3.3 that the number of males was similar in the CheckMate trial and in the SACT cohort (82% versus 81%). Median age in the SACT cohort was slightly older (62 in SACT versus 59 in CheckMate), which was consistent with the larger proportion of those in the older age groups.[2, 5]

As regards ECOG performance status, the numbers with a PS of 0 were fairly similar (20% in CheckMate versus 24% in SACT) but there were more patients with PS of 1 in CheckMate (79% versus 57%). Only one patient (0.4%) in CheckMate had a PS of 2 or more (inclusion criteria for CheckMate was PS of 0 or 1). The SACT cohort had 29 patients with a PS of 2 and four patients with a PS of 3 (7% overall). Thirteen percent of the SACT data were missing so it is possible that some of these patients had a higher PS status. It was not possible to estimate comparability in terms of breakdown of PD-L1 scores as 42% of SACT scores were not recorded. Additionally, both the trial and the SACT cohort had over 30% of scores which could not be quantified.

ERG comment: Although the baseline characteristics between the arms for the all-randomised population are comparable, a comparison of baseline characteristics between the arms for the docetaxel subgroup could be valuable. This was requested as an additional clarification question, which the company did not provide (see Section 2.2).[5] Taking the SACT cohort as being typical of patients to be seen in clinical practice, UK patients might be slightly older and a small number will have a worse performance status than the patients in the all-randomised CheckMate 141 trial. Assuming that other disease characteristics and prior therapies are similar between the two data sources, it might be expected that UK patients do slightly worse than patients in the CheckMate 141 trial. However, this does not appear to be the case looking at the SACT data (see Section 3.2).

Table 3.1: Summary of methodology of CheckMate 141 trial and SACT dataset

Trial name	CheckMate 141	SACT dataset
Location	International: 55 study sites across 15 countries in North America (USA and Canada), South America, Europe and Asia. Five study sites were included in the UK, with a total of 34 patients randomised to study treatment at UK sites.[10]	UK
Design	Multicentre, open-label, phase III randomised controlled trial	Observational study
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[11] • 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	*Key inclusion criteria:* • ECOG performance status of 0 or 1 and would otherwise be potentially fit for docetaxel-based or methotrexate-based 2nd line chemotherapy • Histologically confirmed R/M SCCHN not amenable to local therapy with curative intent. (surgery and/or radiation therapy with or without chemotherapy.) • Tumour progression or recurrence within 6 months of last dose of platinum therapy (*as adjuvant chemotherapy; neo-adjuvant chemotherapy; concurrent with radiotherapy; or palliative chemotherapy for recurrent or metastatic disease) • Not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody • Every effort has been made for the patient to have PD-L1 testing with an approved and validated test to determine the Tumour Proportion Score (TPS)

Trial name	CheckMate 141	SACT dataset
	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	
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 (IC) (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). 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., QW) 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.	*Nivolumab only (n=556)* Nivolumab (i.v. infusion, Q2W) Dosing started as weight base (3 mg/kg) and then changed to a flat dose (240 mg) in response to the licence. Six patients did not receive treatment and 44 patients died before treatment.
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	*OS* *Treatment duration (TTD)*

Trial name	CheckMate 141	SACT dataset
	withdrawal of study consent after patients discontinued study treatment.	
Secondary and other outcomes	*Secondary endpoints:* Progression-free survival (PFS) Time to discontinuation (TTD) 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	Reason for stopping treatment ('Treatment outcomes for patients that have ended treatment')
Subgroups	A pre-planned exploratory subgroup analysis of OS by treatment group and PD-L1 expression (≥1% or <1%) was conducted.	A subgroup analysis of OS by PD-L1 expression level was conducted.
Duration of study and follow-up	The study was initiated on the 29th May 2014 with the last patient's 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.	Entry to the SACT dataset from 13 October 2017 to 12 May 2019. A snapshot of SACT data was taken on 5 October 2019 and made available for analysis on the 14 October 2019. The snapshot includes SACT activity up to the 30 June 2019. Tracing the patients' vital status was carried out on 11 October 2019 using the personal demographics service (PDS).[9] The median follow-up time was 83.5 days.

Source: CS,[2] and SACT dataset report.[9] except *provided in an e-mail from NICE.[12]

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 1.1 = Response Evaluation Criteria In Solid Tumours version 1.1; 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 3.2: 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)	61.0 (28–74)	61.0 (32–78)	57.0 (39–78)
Age categorisation, n (%)					
<65	172 (71.7)	76 (62.8)	34 (63.0)	32 (61.5)	10 (66.7)
≥65 and <75	56 (23.3)	39 (32.2)	20 (37.0)	16 (30.8)	3 (20.0)
≥75	12 (5.0)	6 (5.0)	0	4 (7.7)	2 (13.3)
Male, n (%)	197 (82.1)	103 (85.1)	45 (83.3)	44 (84.6)	14 (93.3)
Race, n (%)					
White	196 (81.7)	104 (86.0)	50 (92.6)	41 (78.8)	13 (86.7)
Black/African American	10 (4.2)	3 (2.5)	0	2 (3.8)	1 (6.7)
Asian	29 (12.1)	14 (11.6)	4 (7.4)	9 (17.3)	1 (6.7)
Other	5 (2.1)	0	0	0	0
Region, n (%)					
North America	101 (42.1)	44 (36.4)	12 (22.2)	19 (36.5)	13 (86.7)
Europe	109 (45.4)	62 (51.2)	37 (68.5)	25 (48.1)	0
Rest of the world	30 (12.5)	15 (12.4)	5 (9.3)	8 (15.4)	2 (13.3)
Tobacco use, n (%)					
Current/former	191 (79.6)	85 (70.2)	40 (74.1)	35 (67.3)	10 (66.7)
Never	39 (16.3)	31 (25.6)	11 (20.4)	15 (28.8)	5 (33.3)
Unknown	10 (4.2)	5 (4.1)	3 (5.6)	2 (3.8)	0
Disease characteristics					
Site of primary tumour, n (%)[b]					
Oral cavity	108 (45.0)	67 (55.4)	29 (53.7)	31 (59.6)	7 (46.7)

Characteristic	Nivolumab (n=240)	IC (n=121)	Docetaxel (n=54)	Methotrexate (n=52)	Cetuximab (n=15)
Pharynx	92 (38.3)	36 (29.8)	19 (35.2)	11 (21.2)	6 (40.0)
Larynx	34 (14.2)	15 (12.4)	5 (9.3)	8 (15.4)	2 (13.3)
Other	6 (2.5)	3 (2.5)	1 (1.9)	2 (3.8)	0
HPV p-16 status, n (%)					
Positive	63 (26.3)	29 (24.0)	16 (29.6)	9 (17.3)	4 (26.7)
Negative	50 (20.8)	36 (29.8)	19 (35.2)	15 (28.8)	2 (13.3)
Not tested[c]	127 (52.9)	56 (46.3)	19 (35.2)	28 (53.8)	9 (60.0)
Prior therapy					
Number of lines of prior systemic cancer therapy, n (%)					
1	106 (44.2)	58 (47.9)	29 (53.7)	21 (40.4)	8 (53.3)
2	80 (33.3)	45 (37.2)	19 (35.2)	19 (36.5)	7 (46.7)
≥3	54 (22.5)	18 (14.9)	6 (11.1)	12 (23.1)	0
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: ERG report for TA490.[6]

Notes: [a]The investigator had to indicate which IC agent he or she would use if the subject were randomised to 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

Table 3.3: Baseline characteristics of patients in CheckMate 141 compared to the SACT data cohort study

Characteristic	CheckMate 141: Nivolumab (n = 240)	SACT data cohort study (n = 506)
Male, n (%)	197 (82)	411 (81)
Age, median years	59	62
Age categorisation, n (%)		
< 40	14 (6)	15 (3)
40 – 49	18 (8)	39 (8)
50 – 59	90 (38)	145 (29)
60 – 69	87 (36)	194 (38)
70 – 79	29 (12)	104 (21)
80 +	2 (1)	9 (2)
Performance status, n (%)		
0	49 (20)	122 (24)
1	189 (79)	286 (57)
≥ 2	1 (0.4)	33 (7)
Missing	1 (0.4)	65 (13)
PD-L1 score, n (%)		
< 1	73 (30)	55 (11)
≥ 1	88 (37)	52 (10)
Can't be quantified	79 (33)	189 (37)
Not recorded	0	210 (42)

Source: Company submission; Company response to clarification; Public Health England Data Review[2, 5, 9]
Notes: Percentages may not total 100 due to rounding.
PD-L1 = programmed death ligand 1; SACT = Systemic Anti-Cancer Therapy

3.2 Results of the new clinical evidence

3.2.1 Overall survival

An overview of OS in the previous data cut (20th September 2016**)** and new data cut (15th October 2019**)** of CheckMate 141 **and** the SACT data is provided in Table 3.4. From the table it can be seen, that as in the earlier data from CheckMate 141, there is an OS advantage to nivolumab in terms of HR (0.6858 [95% CI, 0.5483 to 0.8579; p<0.001]). The advantage is very similar, albeit slightly greater with the more mature data. Median OS was similar between the earlier and later data cuts of the CheckMate 141 data, the point estimates being identical and showing a longer survival in the nivolumab arm (7.72 months [95% CI: 5.68 to 8.77]) versus the IC arm (5.06 months [95% CI: 4.04 to 6.24]).

The later data cut of the CheckMate 141 trial provides fuller data for 24-month survival and data for 36- and 48-month survival as shown in Table 3.4. The data showed that the survival advantage of nivolumab was maintained at 36 months (10.3% [95% CI: 6.8 to 14.7] versus 2.5% [95% CI: 0.7, to 6.6) and at 48 months (8.0% [95% CI: 4.9 to 12.0] versus 1.7% [95% CI: 0.3, to 5.4).

The Kaplan-Meier (KM) plot for OS based on the latest data cut is presented in Figure 3.1. The IC and nivolumab Kaplan-Meier OS curves overlapped until approximately Month 4 and then separated, favouring nivolumab.

In terms of comparison to the SACT dataset, median OS on nivolumab is higher in CheckMate 141 than the 6.5 months (95% CI: 5.6 to 7.6) of the SACT dataset, although this is reported to be based on a median follow up of only 83.5 days.[9] However, one-year survival rates were similar between the nivolumab arm of the latest CheckMate 141 data and the SACT database (33.4%[95% CI: 27.5 to 39.5]) and 34% [95% CI 29 to 38]).

In terms of OS according to PD-L1 status, for patients with a PD-L1 < 1%, the HR was below 1 and those receiving nivolumab had a longer median survival (6.51 months [95% CI: 4.37 to 11.73]) than those in the IC group (5.45 months [95% CI: 3.68 to 8.54]) but neither of these outcomes were statistically significant. For patients with a PD-L1 ≥ 1%, the HR was lower and statistically significant and median survival was statistically significantly longer with nivolumab (8.15 months [95% CI: 6.67 to 9.53]) than with IC (4.60 months [95% CI: 3.81 to 5.78]). However, as reported in the response to clarification, the interaction between treatment and PD-L1 status in the Cox proportional hazards model was not statistically significant (p = 0.239) indicating that there was no evidence that the treatment effect differed between the different PD-L1 status subgroups.[5] The company indicate that the interpretation of analyses of the PD-L1 subgroups should be made with caution due to the smaller sample sizes (116 for PD-L1 <1% and 157 for ≥ 1%) and wider 95% CI for the HR. The OS curves according to PD-L1 status are presented in Figures 3.2 and 3.3.

.

Table 3.4: Overall survival in the all-randomised population in CheckMate 141 and SACT

Outcome[a]	CheckMate141 20th September 2016		CheckMate141 15th October 2019		SACT 11th October 2019
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=506)
Deaths, n (%)	[redacted]	[redacted]	218 (90.8)	118 (97.5)	335/506 (66.2)
Median OS, months (95% CI)	[redacted]	[redacted]	7.72 (5.68, 8.74)	5.06 (4.04, 6.24)	6.5 (5.6, 7.6)
HR for death with nivolumab (95% CI)	0.70 (97.73% CI: 0.51, 0.96)*		0.6858 (0.5483, 0.8579)		NA
1-year survival rate, % (95% CI)	[redacted]	[redacted]	33.4 (27.5, 39.5)	19.4 (12.9, 26.9)	34 (29, 38)
18-month survival rate, % (95% CI)	[redacted]	[redacted]	22.1 (17.0, 27.6)	8.4 (4.3, 14.3)	NR
24-month survival rate, % (95% CI)	[redacted]	[redacted]	16.8 (12.3, 21.9)	5.9 (2.6, 11.1)	NR
36-month survival rate, % (95% CI)	[redacted]	[redacted]	10.3 (6.8, 14.7)	2.5 (0.7, 6.6)	NR
48-month survival rate, % (95% CI)	[redacted]	[redacted]	8.0 (4.9, 12.0)	1.7 (0.3, 5.4)	NR

Source: Tables 5 and 8 CS[2] except *ERG report for TA490.[6]
HR = hazard ratio; IC = investigator choice; NA = not available

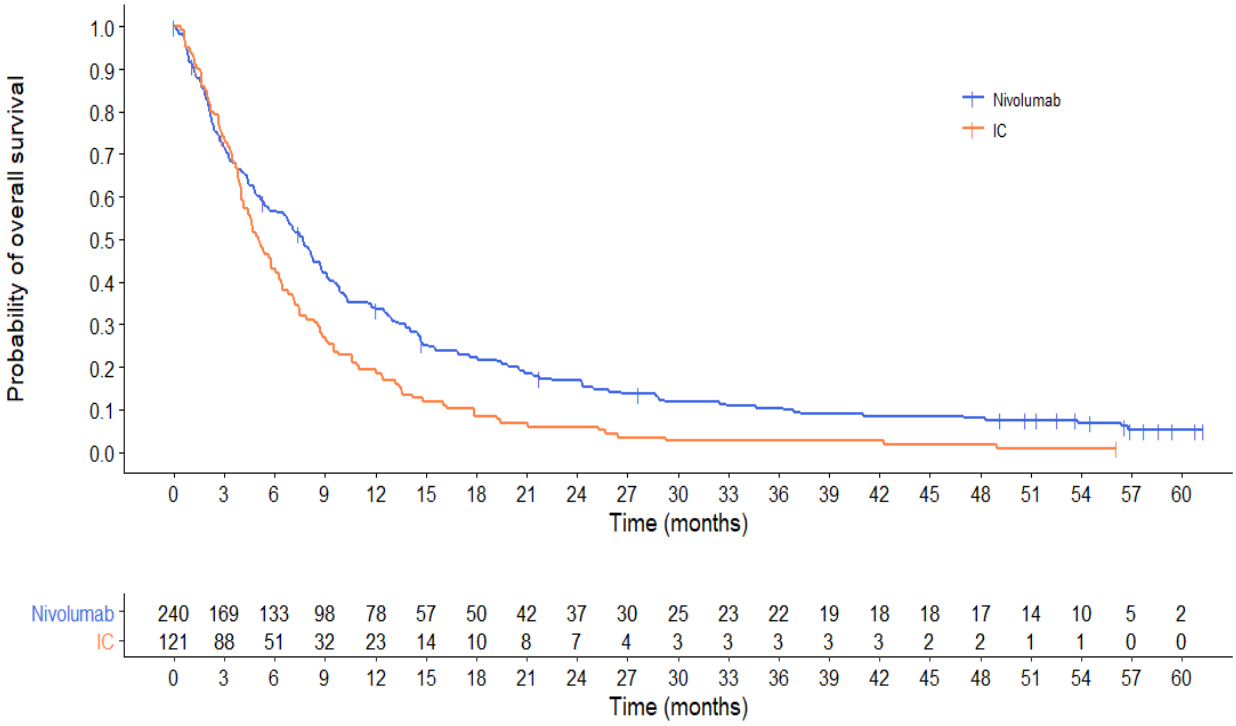
Table 3.5: Overall survival according to PD-L1 status in CheckMate 141 and SACT

Outcome[a]	CheckMate141 PD-L1 <1% 15 October 2019		CheckMate141 PD-L1 ≥1% 15 October 2019		SACT 11th October 2019
	Nivolumab (n=76)	IC (n=40)	Nivolumab (n=96)	IC (n=61)	Nivolumab (n=506)
Deaths, n (%)	72/76 (94.7)	40/40 (100)	87/96 (90.6)	60/61 (98.4)	NR
Median OS, months (95% CI)	6.51 (4.37, 11.73)	5.45 (3.68, 8.54)	8.15 (6.67, 9.53)	4.60 (3.81, 5.78)	NR
HR for death with nivolumab (95% CI; p-value)*	0.7429 (0.5015, 1.101; p=0.138)		0.5397 (0.3857, 0.7554; p<0.001)		NR

Source: Tables 8, 9, of the CS and Table 5 of the CS appendix.[2, 13]

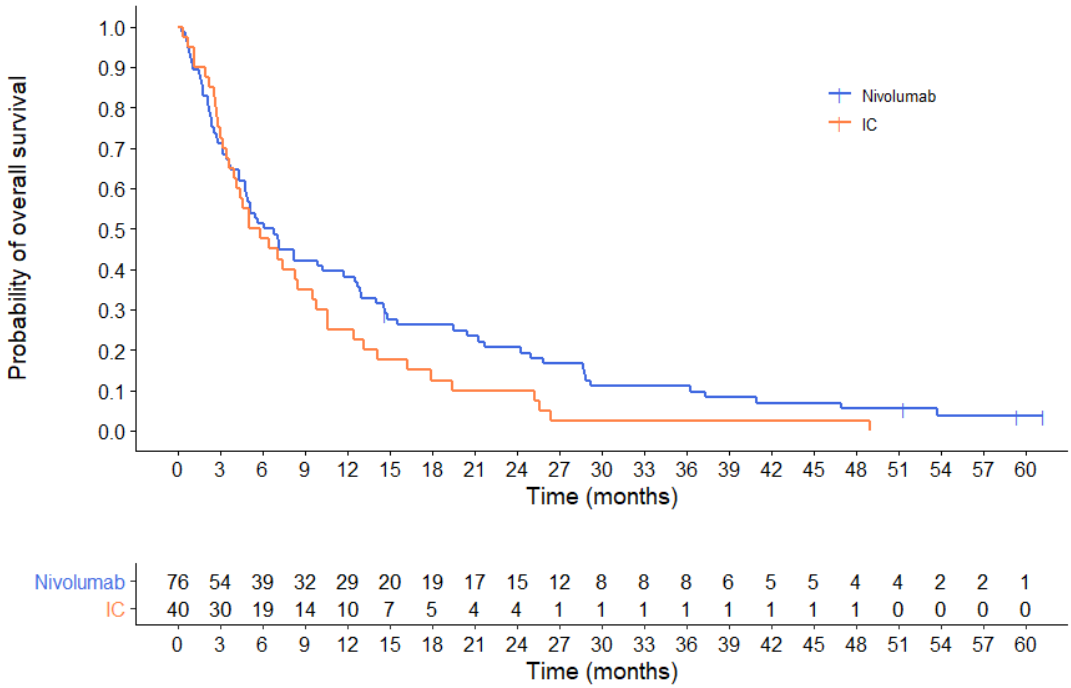
* Computed using unstratified Cox proportional hazards model with treatment group as the sole covariate.

Figure 3.1: Kaplan-Meier plot for overall survival in CheckMate 141



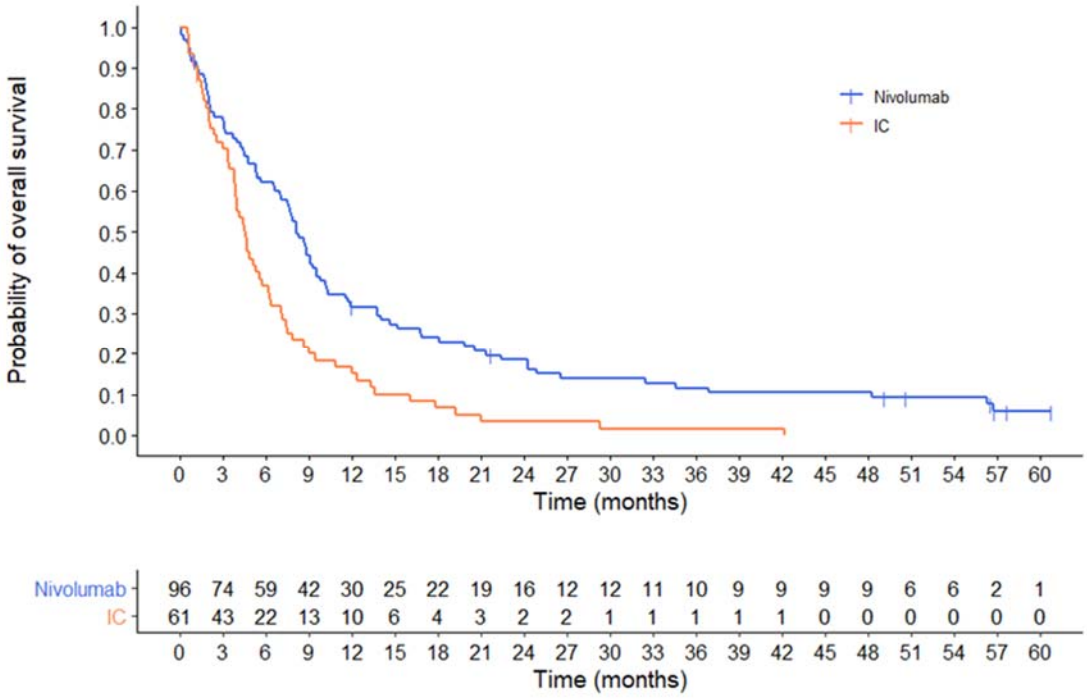
Data cut-off: 15 October 2019
Abbreviations: IC: investigator's choice.
Source: Company submission, Figure 1.[2]

Figure 3.2: Kaplan-Meier plot for overall survival for patients with the PD-L1 <1% in CheckMate 141



CheckMate 141 data cut-off: 15 October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: Company submission, Figure 5.[2]

Figure 3.3: Kaplan-Meier plot for overall survival for patients with the PD-L1 ≥1% in CheckMate 141



CheckMate 141 data cut-off: 15 October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: Company submission, Figure 6.[2]

ERG comment:

- The committee had specific concerns about the OS benefit beyond two years and expected to see further evidence. In relation to this the ERG noted that the company presented data from the 15 October 2019 data cut which had a minimum follow up of 48.2 months. Results presented above showed that the survival advantage of nivolumab over IC was maintained in terms of HR and median survival and continued through 36 months and at 48 months.
- However, the ToE stipulated that docetaxel should be the comparator and so the ERG requested in the clarification letter for analyses in the docetaxel subgroup to be presented, the response to which was not to provide these (see Section 2.2).[5]
- Although patients in the SACT data set had a lower median survival (6.5 vs. 7.7 months) than those in the nivolumab arm of Check Mate 141, it is important to note that this was based on a much shorter median follow-up of 83.5 days and the 95% CIs overlapped. Also, one-year survival rates were very similar (34% and 33.4%).
- The committee also had concerns regarding the evidence of the benefit of nivolumab for those with PD-L1 expression < 1%. CheckMate 141 was not powered to detect differences in benefit according to PD-L1 status. However, the company presented data according to PD-L1 status as requested by the committee based on the updated 15 October 2019 data cut providing four-year results. This showed that patients with a PD-L1 < 1% had a reduced hazard of death on nivolumab compared with IC but this was not statistically significant. For patients with a PD-L1 ≥ 1% the hazard of death was significantly reduced with nivolumab. However, there was no significant evidence of a treatment and subgroup interaction (p = 0.239) and these results should be considered with caution due to the reduced sample sizes and wider confidence intervals.

3.2.2 Progression-free survival

An overview of PFS in the previous data cut (20 September 2016**)** and new data cut (15 October 2019**)** of CheckMate 141 is presented in Table 3.6 From the table it can be seen, that, as for OS, there was little change with the HR of 0.82 (0.65, 1.02; p=0.0766) showing a slightly greater advantage for nivolumab than previously. [redacted], showing a shorter median PFS in the nivolumab arm than in the IC arm (2.04 months [95% CI:1.91 to 2.14] versus 2.33 months [1.94, 3.06]).

As explained by the company, there was delayed separation of the Kaplan-Meier curves using the CheckMate 141 data (see Figure 3.4) which showed that by six months the estimated PFS rate was higher in the nivolumab arm than the IC arm.(20.4% [95% CI:15.4 to 26.0] versus 10.2% [95% CI: 5.2 to 17.2]).

Progression-free survival data was not required to be collected in the SACT data set.

In terms of PFS according to PD-L1 status, the PD-L1 <1% group receiving nivolumab had a shorter median PFS than those in the IC arm (1.95 months [95% CI: 1.87 to 2.14 versus 2.68 months [95% CI: 1.97, 4.63]) (see Table 3.7). The PD-L1 ≥ 1% group receiving nivolumab had a numerically longer PFS than those in the IC arm (2.14 months [95% CI: 1.97 to 3.45 versus 1.97 months [95% CI: 1.84, 3.06]). The ERG requested the results of analyses including an interaction term between treatment and PD-L1 status. The company response to clarification showed that there was weak evidence of an interaction (p=0.077) indicating that the treatment effect of nivolumab differed between the groups based on PD-L1 status, although the HRs were not reported.[5]

Table 3.6: Progression Free Survival in the all-randomised population in CheckMate 141

Outcome[a]	CheckMate141 20 September 2016		CheckMate141 15 October 2019	
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)
Events, n (%)	[redacted]	[redacted]	214 (89.2)	104 (86.0)
Median PFS, months (95% CI)	[redacted]	[redacted]	2.04 (1.91, 2.14)	2.33 (1.94, 3.06)
HR for progression or death with nivolumab (95% CI; p-value)	[redacted]		0.82 (0.65, 1.02; p=0.0766)	
6-month PFS rate, % (95% CI)	[redacted]	[redacted]	20.4 (15.4, 26.0)	10.2 (5.2, 17.2)
1-year PFS rate, % (95% CI)	[redacted]	[redacted]	9.5 (6.0, 14.0)	2.6 (0.5, 8.0)
18-month PFS rate, % (95% CI)	[redacted]	[redacted]	8.5 (5.2, 12.8)	NA
24-month PFS rate, % (95% CI)	[redacted]	[redacted]	7.5 (4.5, 11.7)	NA

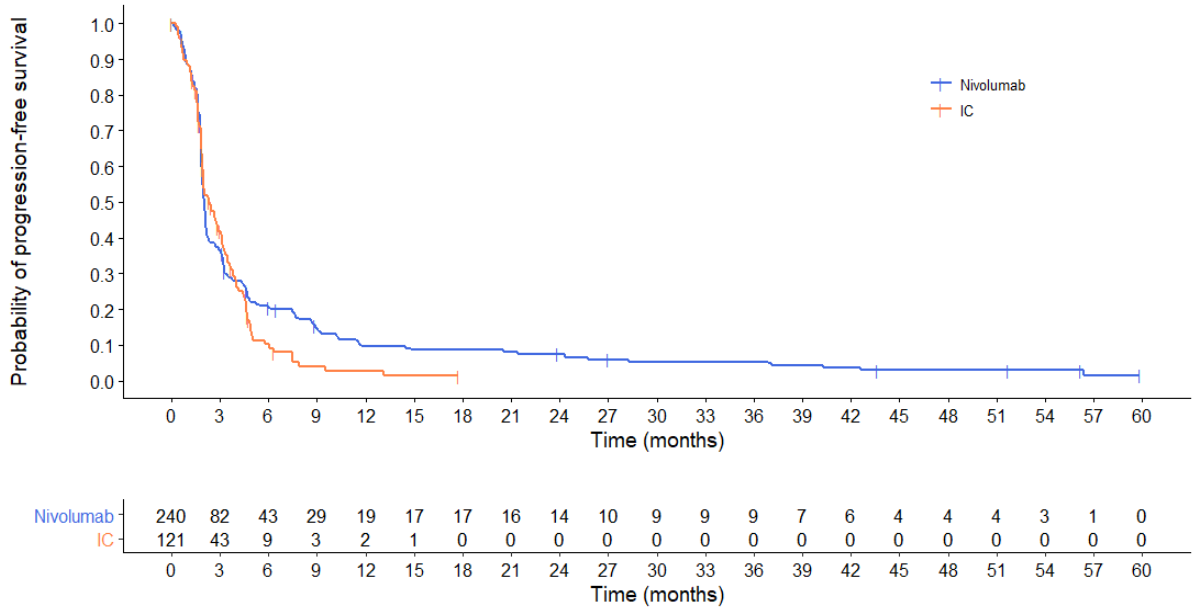
Source: Table 6 CS;[2] 1.1 addendum ERG report.[6]
HR = hazard ratio; IC = investigator choice; NA = not assessed; PFS = progression-free survival

Table 3.7: Progression Free Survival by PD-L1 status

Outcome[a]	CheckMate141 PD-L1 < 1%		CheckMate141 PD-L1 ≥ 1%	
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)
Events, n (%)	69/76 (90.8)	36/40 (90.0)	88/96 (91.7)	54/61 (88.5)
Median PFS, months (95% CI)	1.95 (1.87, 2.14)	2.68 (1.97, 4.63)	2.14 (1.97, 3.45)	1.97 (1.84, 3.06)
HR	NR		NR	

Source: Table 10 CS.[2]
HR = hazard ratio; IC = investigator choice; NA = not assessed; PFS = progression-free survival

Figure 3.4: Kaplan-Meier plot for progression-free survival in the all-randomised population in CheckMate 141



Data cut-off: 15 October 2019
Abbreviations: IC: investigator's choice.
Source: Company submission, Figure 2.[2]

ERG comment:

- Concerns about PFS were not specifically mentioned in the ToE and PFS data were not required to be collected in the SACT dataset. However the company provided the up to date data (15 October 2019) from CheckMate 141 on PFS and the ERG can confirm that there was no fundamental change in the conclusion that the PFS advantage to nivolumab versus IC in terms of HR, although not statistically significant, was maintained and the advantage to IC in terms of median survival, although small, was also maintained.
- The company was not explicitly required to present data by PD-L1 status for PFS and as stated before CheckMate 141 was not powered to detect differences by PD-L1 status. HRs were not provided for PFS for the PD-L1 subgroups, but the median PFS estimates indicated that there were no significant differences in PFS between nivolumab and IC in patients with PD-L1 <1% or those with PD-L1 ≥ 1%.

3.2.3 Time to treatment discontinuation

The latest CheckMate 141 data cut provides data from a minimum follow-up of 48.2 months (representing 36.8 additional months of follow-up). At the time of this data cut-off, the company stated that 13 patients in the nivolumab arm and one patient in the IC arm were still alive and in follow-up, with [redacted] still on treatment. Median TTD was similar between the CheckMate 141 earlier data cut and the later data cut. It was also similar between nivolumab and IC arms in the trial [redacted] (Table 3.8). The company showed in Kaplan-Meier curves that there was separation of the curves favouring nivolumab from approximately [redacted] months.

The SACT data showed a longer median TTD of 3.0 months (95% CI: 2.7 to 3.3) with no overlap in the 95% CIs. The company also noted that at six months 28% of SACT patients were still receiving treatment as opposed to [redacted]% of the CheckMate 141 patients and at 12 months 17% of patients in the SACT database were still receiving treatment as opposed to [redacted]% of the CheckMate 141 patients.

For PD-L1 < 1% median TTD in CheckMate 141 was virtually identical between treatment groups and similar to the overall result at [redacted] for nivolumab versus [redacted] for IC (Table 3.9). In the PD-L1 ≥ 1 group the median TTD was higher in the nivolumab group than the IC group of CheckMate 141 at [redacted] The response to clarification showed that there was a statistically significant interaction (p=0.0208) in the Cox proportional hazards model between treatment and PD-L1 subgroup indicating that the treatment effect was different in patients with PD-L1 < 1% compared to ≥ 1%, although the HRs were not reported.[5]

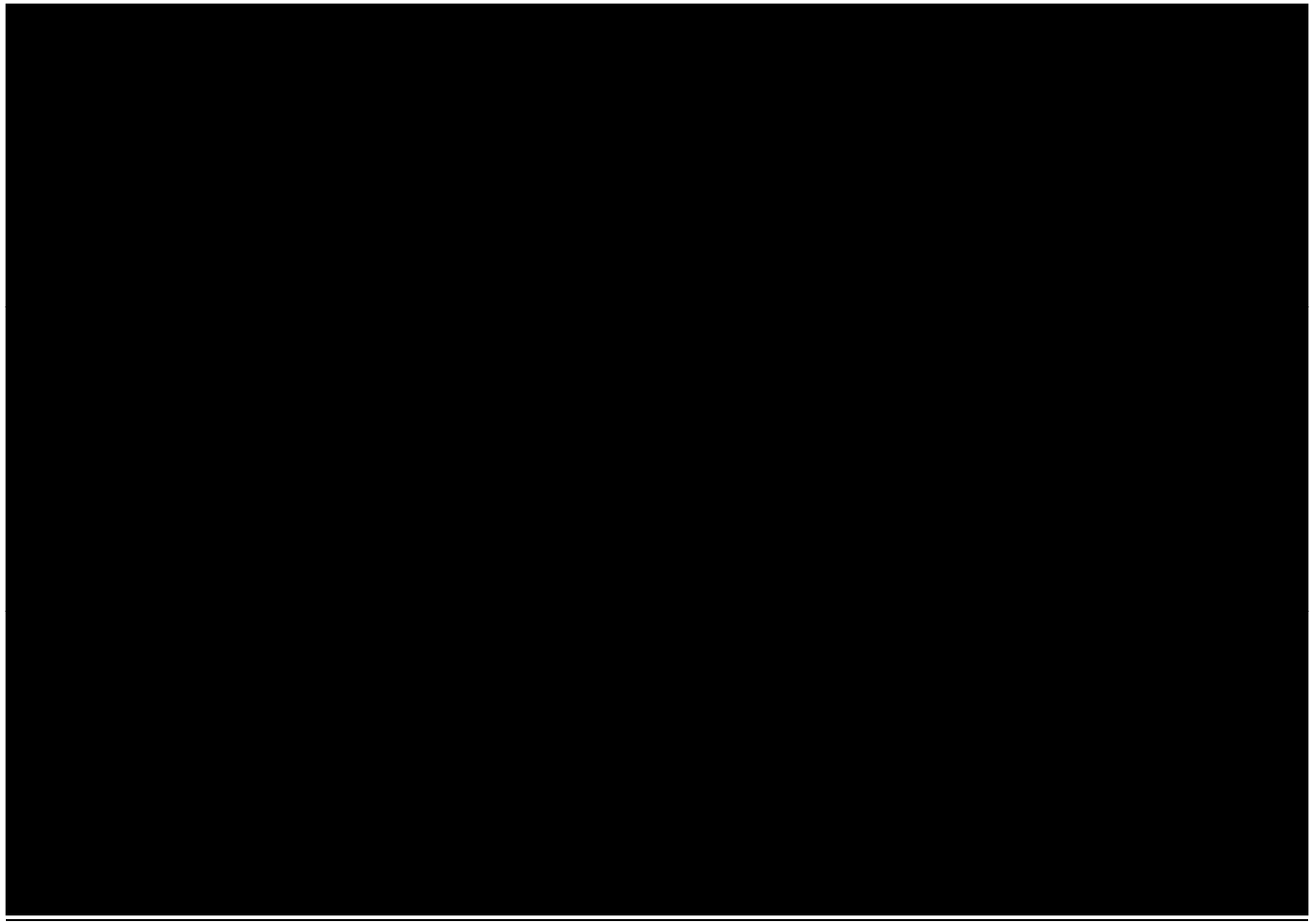
Table 3.8: Time to treatment discontinuation in CheckMate 141 and SACT

Outcome[a]	CheckMate141 20 September 2016		CheckMate141 15 October 2019		SACT 11 October 2019
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=506)
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	394/506
Median TTD, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	3.0 (2.7, 3.3)
Source: Tables 7 CS; Addendum to ERG report.[2, 6]					

Table 3.9: Time to treatment discontinuation by PD-L1 status in CheckMate 141 and SACT

Outcome[a]	CheckMate141 PD-L1 <1%		CheckMate141 PD-L1 ≥1%		SACT 11 October 2019
	Nivolumab (n=73)	IC (n=38)	Nivolumab (n=88)	IC (n=61)	Nivolumab (n=506)
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR
Median TTD, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	NR
Source: Table 11 of the CS.[2]					

Figure 3.5: Kaplan-Meier comparing time to discontinuation in CheckMate 141 and the SACT database



CheckMate 141 data cut-off: 15 October 2019
Abbreviations: SACT: Systemic Anti-Cancer Therapy.
Source: Company submission, Figure 12;[2] Public Health England report[9]

Figure 3.6: Kaplan-Meier plot for time to treatment discontinuation for patients with the PD-L1 <1% in CheckMate 141

CheckMate 141 data cut-off: 15 October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: Company submission, Figure 9.[2]

Figure 3.7: Kaplan-Meier plot for time to treatment discontinuation for patients with the PD-L1 ≥1% in CheckMate 141

CheckMate 141 data cut-off: 15 October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: Company submission, Figure 10.[2]

ERG comment

- Concerns about TTD were not specifically mentioned in the ToE. However, the company provided the up to date data (15 October 2019) from CheckMate 141 on TTD which the ERG has presented above and the ERG noted that median TTD was similar between the earlier and later data cuts of the CheckMate 141 data.
- However, [redacted], the median TTD was shorter than in the SACT data (three months). It is unclear to the ERG why this was and what the implications for generalisability of the effectiveness of nivolumab in terms of OS or PFS might be. OS seemed to be slightly shorter in the SACT dataset, although this was very uncertain. It might seem to indicate that more drug needed to be given to obtain the same OS, but this is unclear.
- The company was not explicitly required to present data by PD-L1 status for TTD and, as stated before, CheckMate 141 was not powered to detect differences by PD-L1 status. [redacted]

3.2.4 Health-related quality of life

The committee had requested an exploration of the most appropriate utility values in the light of new evidence. However, the company used the EQ-5D data from the 20 September 2016 data cut of the CheckMate 141 trial to analyse how utility might change over time and how utility might change with respect to how close patients were from death. Details of the generation of the utility values and a discussion of their appropriateness can be found in the cost-effectiveness section of this report.

3.2.5 Adverse effects of treatment

No specific requirements were asked of the company regarding an update of AE data and the SACT study did not collect such data either. For completeness of reporting the ERG asked the company to provide AE data from the 15 October 2019 data cut as per the original submission. Table 3.10 provides a high-level summary, which compares the new with the September 2016 data cut.

Table 3.10: Summary of adverse events from CheckMate 141

Adverse event, n (%)	Nivolumab (n=236) September 2016		IC (n=111) September 2016		Nivolumab (n=236) 15 October 2019		IC (n=111) 15 October 2019	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
All causality AEs	232 (98.3)	113 (47.9)	109 (98.2)	69 (62.2)	232 (98.3)	117 (49.6)	109 (98.2)	70 (63.1)
Drug-related AEs	146 (61.9)	36 (15.3)	88 (79.3)	40 (36.0)	146 (61.9)	37 (15.7)	88 (79.3)	41 (36.9)

Source: Company response to clarification.[5]
AEs = adverse events; CS = company submission; IC = investigator's choice

The most frequently reported grade 3-4 AEs in the nivolumab arm were also reported in the response to clarification, which the ERG can confirm were those found to be most common during TA490.[5, 14] These are (15 October 2019 vs. September 2016 data cuts):

- Anaemia: (17, 7.2%) vs. (15, 6.4%),
- dyspnoea (13, 5.5%) vs. (13, 5.5%),
- hyponatraemia (13, 5.5%) vs. (11, 4.7%),
- pneumonia (12, 5.1%) vs. (11, 4.7%) and
- malignant neoplasm progression (11, 4.7%) vs. (11, 4.7%)

ERG comment: It appears that little has changed in both the number and percentage of AEs between TA490 and the CDF review, which leads to the same conclusion as found by the ERG in TA490, i.e. 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.

3.3 Summary of the new clinical effectiveness evidence according to the terms of engagement for the CDF review

The ToE stated that OS from CheckMate 141 data was to be updated. The ERG can confirm that this has been done with the latest data cut being 15 October 2019, i.e. four years follow-up. The results show that the survival advantage of nivolumab over IC was maintained in terms of HR and median survival and continued through 36 months and at 48 months. Also, the company provided the up to date data from CheckMate 141 on PFS and the ERG can confirm that the numerical advantage to nivolumab versus IC was maintained. Although the ToE did not specify an update in terms of safety, the ERG asked the company to provide up to date AE data and, according to the clarification letter response, it appears that little has changed in both the number and percentage of AEs between TA490 and the CDF review, which leads to the same conclusion as found by the ERG in TA490, i.e. 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.

However, given that the committee also concluded that the comparator should be docetaxel, the ERG considers that the most appropriate evidence of effectiveness and safety versus docetaxel is that from the docetaxel subgroup, which the company did not provide in either the CS or in response to the clarification letter (see Section 2.2). The ERG considers that this is a major source of uncertainty that can be resolved by the company.

The SACT dataset, created as a result of the ToE, permits to some degree a test of the generalisability of the outcomes observed in the CheckMate 141 trial in the nivolumab arm to UK clinical practice, at least in terms of the outcomes that were analysed from it, i.e. OS and TTD. Indeed, a comparison reveals that UK patients might be slightly older and a small number will have a worse performance status than the patients in the all-randomised CheckMate 141 trial, which might suggest that UK patients do slightly worse than patients in the CheckMate 141 trial. However, although patients in the SACT data set had a numerically lower median survival than those in the nivolumab arm of Check Mate 141, it is important to remember that this was based on a much shorter median follow-up and the 95% CIs overlapped. Also, one-year survival was very similar. As mentioned with regards to the comparison between nivolumab and docetaxel, it could be argued that the nivolumab arm of the docetaxel subgroup of CheckMate 141 should be used to compare with the SACT dataset. On the other hand, the all-randomised population might be closer to those patients who would be treated with nivolumab in UK clinical practice. This was the judgment of the committee, who concluded that the CheckMate 141 results (implying the all-randomised population) are relevant to the population of interest, i.e. adults

with recurrent or metastatic SCCHN that progressed within six months of platinum-based therapy, in either the early or locally advanced disease stage. Although there is a discrepancy between descriptions of eligibility criteria, those for the SACT dataset could also be regarded as essentially the same as those for CheckMate 141. However, clearly not everyone in CheckMate 141 was found to be eligible for docetaxel according to the IC design. In particular, some were chosen to receive methotrexate, which in the ToE states that it is only for patients who are not fit to have a taxane. The implication of this should be that the population specified for this CDF review and in the SACT dataset should not be aligned with the all-randomised population, but should at least exclude those who would be ineligible for docetaxel. This apparent mismatch between the population and the comparator specified in the ToE does produce some uncertainty in the generalisability of the CheckMate 141, which might be reduced by a comparison of the baseline characteristics and OS in the nivolumab arm of the docetaxel subgroup and the SACT dataset.

In terms of PD-L1 status, nivolumab showed an advantage in terms of OS in comparison to IC for both groups, but it was larger for those with PD-L1 ≥ 1% and only statistically significant in terms of the HR for this subgroup. However, there was no significant evidence of a treatment and subgroup interaction (p=0.239) and these results should be considered with caution due to the reduced sample sizes and wider confidence intervals. For PFS, HRs were not provided for the PD-L1 subgroups, but the median PFS estimates indicate that there were no significant differences in PFS between nivolumab and IC in patients with PD-L1 <1% or those with PD-L1 ≥ 1%. There was also evidence of only a weak interaction effect.

[redacted]

4. COST EFFECTIVENESS

4.1 Summary and critique of the company's submitted economic evaluation by the ERG

4.1.1 Model structure

The model structure was unchanged from the TA490 CS and consisted of a cohort-based partitioned survival model with three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death.[2, 6] Disease progression was defined by Response Evaluation Criteria in Solid Tumors version 1.1, which was also used in the CheckMate 141 trial. Moreover, TTD was incorporated while allowing treatment continuation after progression in both treatment arms.

Costs and disutilities associated with AEs were estimated per episode and applied only once, at the beginning of the first cycle. This was 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: According to the ToE for CDF review, the company's model structure is suitable for decision making and it was anticipated that the model structure would not change for the CDF review.[1] Moreover, in its original ERG report (for TA490), the ERG stated that "The model structure is similar to other oncology assessments and seems appropriate for the current decision problem".[6]

4.1.2 Population

The cost effectiveness analysis considers patients with R/M SCCHN who have progressed within six months after platinum-based therapy. The company states this is consistent with the study population of the CheckMate 141 trial, because this population underpins the marketing authorisation and is a distinct subset of the population whose disease has progressed after platinum-based therapy.

In the ToE, the committee further concluded that there was evidence of nivolumab's benefit in patients with a PD-L1 expression of 1% or more, but that the benefit was less convincing for those with a PD-L1 expression of less than 1%.[1] As a consequence, the committee expected the updated OS evidence from Checkmate 141 to include analyses by PD-L1 expression. The company provided additional subgroup analyses according to PD-L1 expression level.[2]

ERG comment: The focus on the study population of the CheckMate 141 trial is consistent with the committee preferences stating that the committee concluded that although there are some differences between the trial population and the UK population, the CheckMate 141 results are relevant to the UK population.

4.1.3 Interventions and comparators

As described in Section 2.2, since the original submission for TA490, the licensed dose of nivolumab has been updated to a flat dose of 240 mg every two weeks (Q2W), rather than the weight-based dose used in the CheckMate 141 trial (3 mg/kg every two weeks). The recommended dosage of nivolumab in this indication is 240 mg flat dose every two weeks. The licence also specifies that nivolumab treatment should be continued until treatment is no longer tolerated or clinical benefit is no longer observed. This latter aspect of anticipated use with nivolumab is reflected through the use of the TTD curve to model time on treatment instead of the PFS curve.

According to the company, in the UK, 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.[2] Single-agent docetaxel is predominantly used in UK clinical practice, although paclitaxel may also be used for patients who are not fit enough to receive

treatment with docetaxel and have not received prior taxane therapy.[6] However, as stated in Section 2.2, the ToE specifies docetaxel as the main comparator of interest. In the cost effectiveness model, it is assumed that docetaxel is administrated at a dose of 75mg/m^2 every three weeks.

ERG comment: Based on the available evidence, it seems reasonable to assume docetaxel (75mg/m^2) and docetaxel (30 mg/m^2 as in IC of checkmate trial) are equally effective. It is however questionable whether the nivolumab flat dose can be assumed equally effective to weight-based nivolumab (see section 2.2) and whether the effectiveness of docetaxel, the main comparator according to the ToE, is equally effective as the IC from CheckMate 141 (see section 4.1.5).

4.1.4 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.

4.1.5 Treatment effectiveness and extrapolation

Multiple parametric time-to-event models were used to estimate:

- OS;
- PFS and;
- TTD.

These were estimated based on the nivolumab arm and the investigator's choice (IC) arm of the CheckMate 141 trial (data cut-off: October 15 2019). The IC arm did include treatment with docetaxel, methotrexate and cetuximab. The estimated OS, PFS and TTD based on the IC arm were assumed by the company to be applicable to docetaxel, methotrexate and paclitaxel.

The following parametric survival distributions were examined using goodness-of-fit statistics and visual inspection:

- Exponential
- Weibull
- Gamma
- Gompertz
- Log-normal
- Log-logistic
- Generalised-gamma
- Spline models (using 1- and 2-knots)

In addition to the standard parametric and spline models, the company did also explore piecewise models to estimate OS and PFS. This was consistent with the ToE indicating that a piecewise model is expected to be used to extrapolate OS.[1] The piecewise models consisted of the Kaplan-Meier curves up to a specific cut-off, followed by extrapolation for OS using Exponential (cut-offs: 20, 28, 36, 48, 96 weeks) or Log-normal (cut-offs: 20, 36, 48, 96 weeks) distributions while for PFS the piecewise models were extrapolated using Exponential (cut-offs: 12, 16, 20, 28 weeks) or Weibull (cut-off: 12 weeks) distributions.

For OS the proportional hazards assumption did not hold (CS Figure 13; non-parallel lines that cross/overlap), for PFS and TTD this is unclear for the new data-cut. It should however be noted that

the proportional hazards assumption did not hold for PFS and TTD in the original submission (i.e. based on the September 2016 data-cut). 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 4.1. In this table, the lowest AIC/BIC is printed in bold.

Selection of model for overall survival

To select the piecewise model for OS, the visual fit to the Kaplan-Meier curves was considered by the company. Based on this visual assessment, the company considered that the piecewise log-normal distribution provided a better fit than the Exponential distribution and selected the 96-week cut-off point to maximise the use of the observed data (Figures 4.1 and 4.2). Additionally, the company considered the standard parametric survival models to provide plausible alternative models to estimate OS, particularly the log-normal (had the best goodness-of-fit statistics) and log-logistic distributions were considered to be plausible candidates (Figure 4.3).

Long-term waning of overall survival treatment effect

The company preferred to assume no treatment waning, given the maturity of the CheckMate 141 trial data (compared with the September 2016 data cut-off) and since the log cumulative hazard plot for OS indicated diverging curves towards the end of the follow-up period (Figure 4.2). The company stated that, if this trend would continue, the assumption of treatment waning at five-year is not valid.

Selection of model for progression free survival

As per TA490, the company selected the generalised gamma model for estimating PFS as this distribution had a reasonable visual fit, had one of the best statistical fit (when excluding spline models) and did not result in logical inconsistencies (i.e. that PFS was predicted to be higher than OS). The spline models provided a better statistical fit for nivolumab than the standard parametric models, but the best fitting curves often produced logical inconsistencies. Excluding the spline models, the log-normal and log-logistic models provided the best statistical fit for IC but were associated with a poor visual fit to the observed data for nivolumab in the long term. See Figure 4.4 for the visual fit to the Kaplan-Meier curves.

Selection of model for time to treatment discontinuation

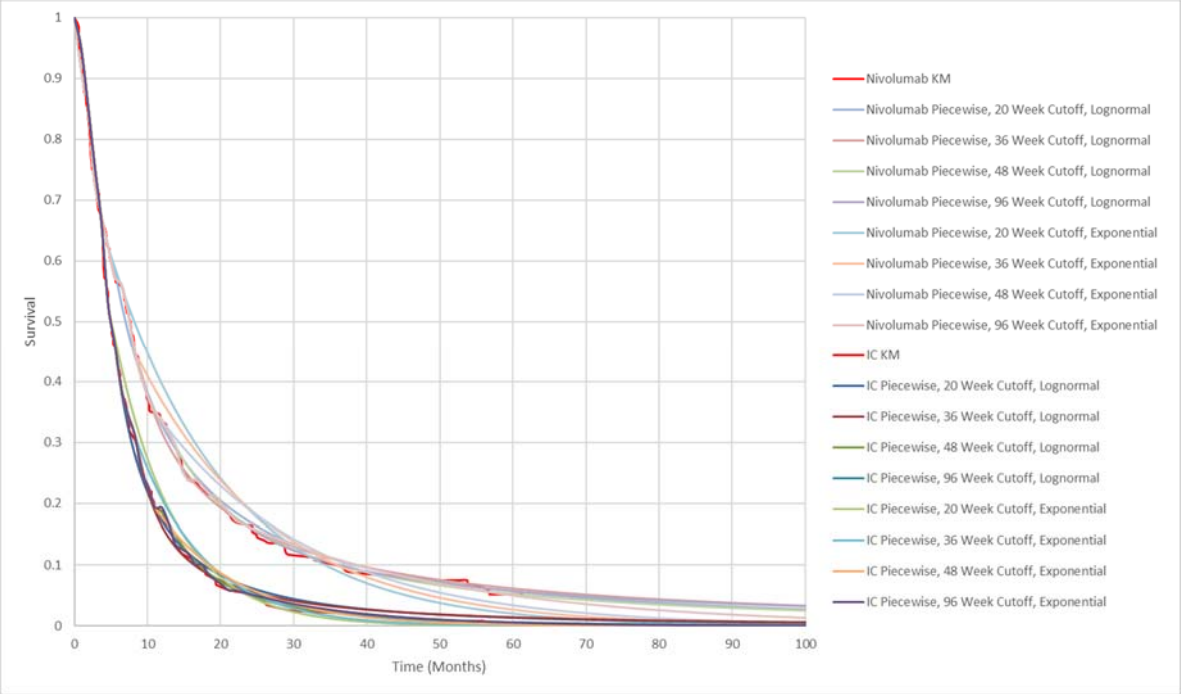
For nivolumab, the two-spline normal model provided the best statistical fit and a reasonable visual fit to the observed data, and was thus considered to be more plausible for extrapolation of TTD than the generalised gamma model used in TA490. The two-spline model also predicted a reasonable estimate of mean TTD when compared to PFS (i.e. mean TTD and mean PFS were similar). [redacted] See Figure 4.5 for the visual fit to the Kaplan-Meier curves.

Table 4.1: Summary of goodness-of-fit data (all-randomised population)

	OS		PFS		TTD	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Nivolumab						
Exponential	1576.347	1579.828	1189.575	1193.056	1239.736	1243.200
Weibull	1564.828	1571.789	1164.921	1171.882	1183.841	1190.768
Gamma	1571.444	1578.406	1184.336	1191.298	1202.061	1208.988
Gompertz	1546.749	1553.711	1106.591	1113.552	1164.232	1171.159
Log-normal	**1540.163**	**1547.124**	1073.288	1080.249	1182.226	1189.154
Log-logistic	1542.166	1549.127	1054.897	1061.858	1160.668	1167.596
Generalised-gamma	1542.155	1552.597	1051.098	1061.540	1171.362	1181.753
Spline models:						
1-Spline Hazard	1544.033	1554.475	1034.038	1044.480	1167.889	1178.281
2-Spline Hazard	1545.414	1559.337	1031.208	1045.130	1152.755	1166.611
1-Spline Odds	1544.082	1554.524	**1021.233**	**1031.675**	1155.359	1165.751
2-Spline Odds	1543.426	1557.349	1022.361	1036.283	1148.706	1162.561
1-Spline Normal	1542.105	1552.547	1038.624	1049.066	1166.073	1176.464
2-Spline Normal	1544.113	1558.036	1027.264	1041.187	**1147.494**	**1161.349**
IC						
Exponential	729.503	732.298	460.787	463.583	419.022	421.732
Weibull	730.838	736.430	446.402	451.994	418.167	423.587
Gamma	728.217	733.809	438.978	444.570	419.407	424.826
Gompertz	729.083	734.674	461.184	466.775	418.815	424.234
Log-normal	**713.309**	**718.901**	433.239	438.830	458.579	463.998
Log-logistic	713.485	719.077	**430.911**	**436.502**	439.908	445.327
Generalised-gamma	715.275	723.662	434.690	443.077	419.038	427.167
Spline models:						
1-Spline Hazard	715.287	723.674	434.421	442.808	416.997	425.126
2-Spline Hazard	717.127	728.310	435.534	446.717	**411.662**	422.500
1-Spline Odds	715.426	723.814	432.689	441.076	413.240	**421.369**
2-Spline Odds	717.326	728.509	434.637	445.820	414.945	425.784
1-Spline Normal	715.207	723.594	434.211	442.599	413.987	422.115
2-Spline Normal	716.381	727.565	434.917	446.100	434.917	445.755

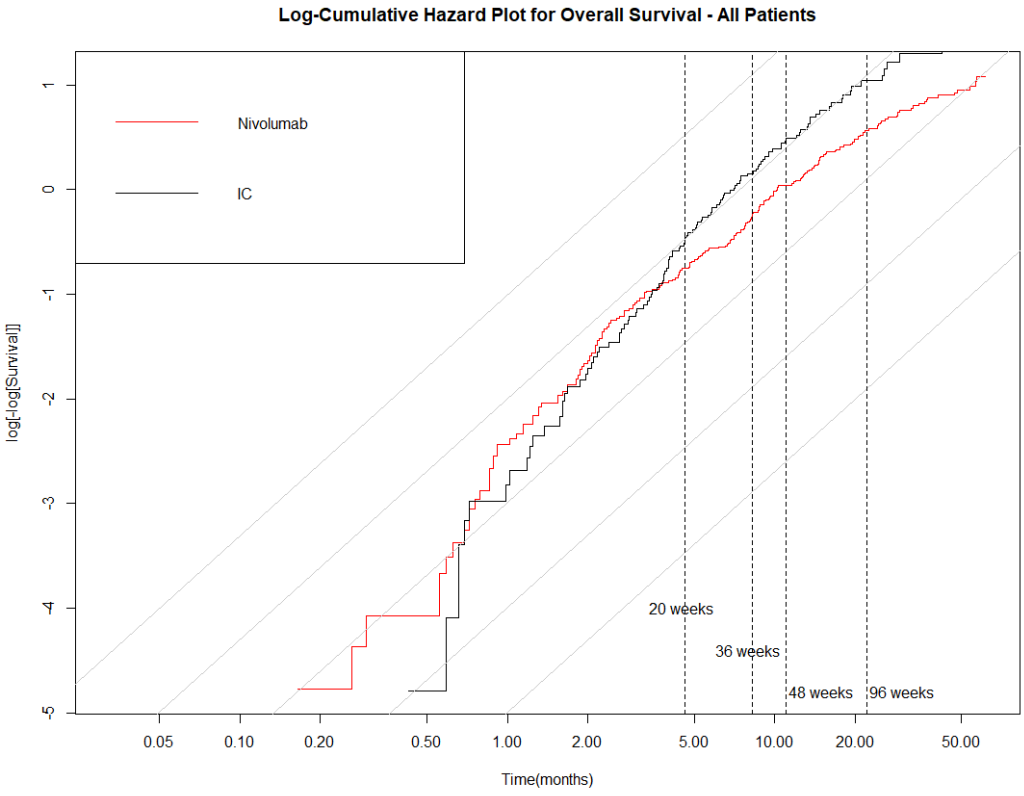
Source: Based on CS Appendix B and the economic model
Note: the lowest AIC/BIC is printed in bold.
AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CS = company submission; IC = investigator's choice; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation

Figure 4.1: OS Kaplan-Meier with piecewise models



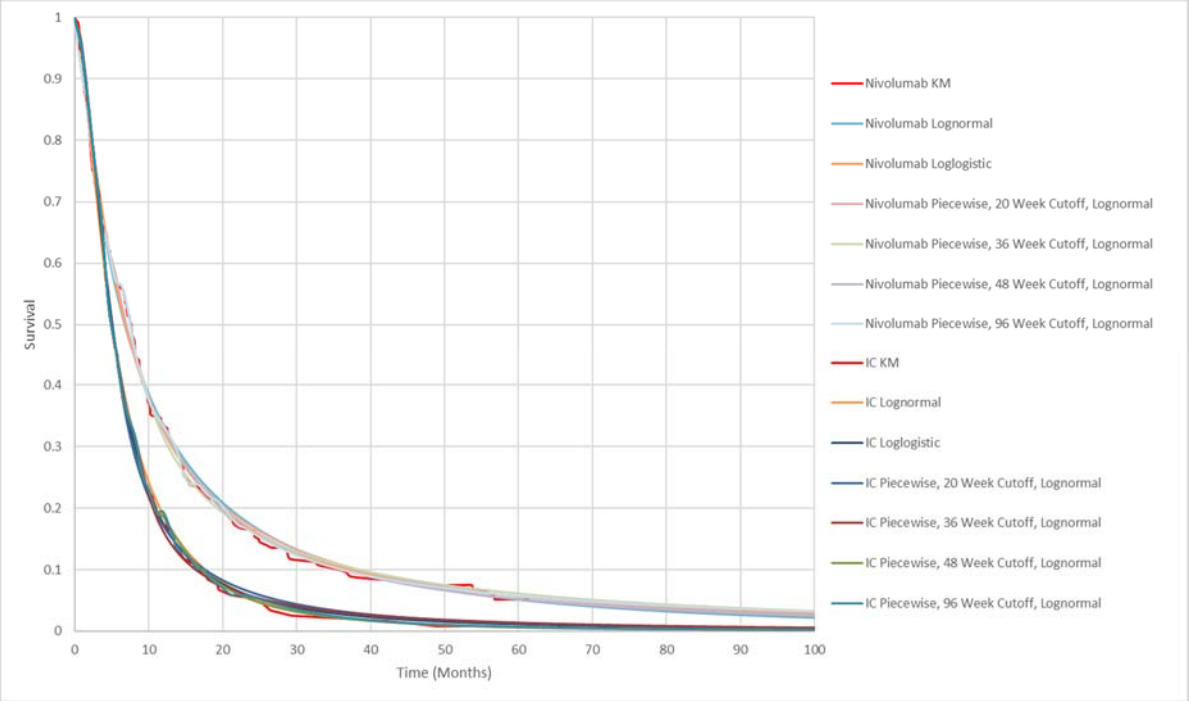
Source: CS Figure 14[2]

Figure 4.2: Log cumulative hazard plot for overall survival



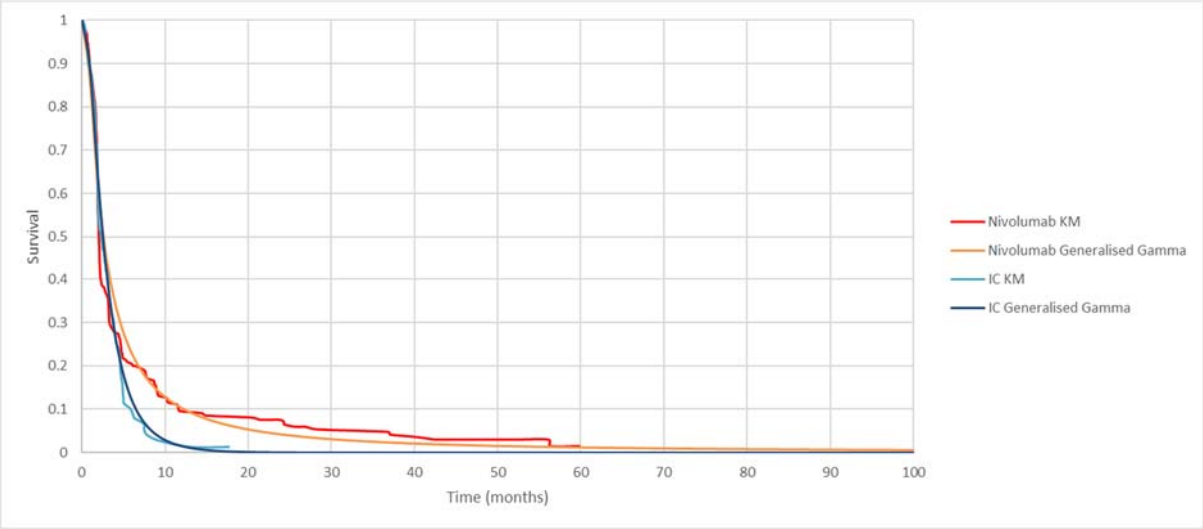
Source: CS Figure 13[2]

Figure 4.3: OS Kaplan-Meier with selected piecewise model and alternative parametric models



Source: CS Figure 15[2]

Figure 4.4: PFS Kaplan-Meier with generalised Gamma model



Source: CS Figure 16[2]

Figure 4.5: TTD Kaplan-Meier with generalised Gamma and two-spline normal model

[redacted]

Source: CS Figure 17

Plausibility of selected distribution for extrapolation

The company did not report on the plausibility of the selected distributions for extrapolation.

Selection of model for patient subgroups based on PD-L1 <1% and ≥1%

[redacted]

For patients with PD-L1 <1% and ≥1% receiving nivolumab, the piecewise method was used to extrapolate OS from the latest data cut of the CheckMate 141 trial. As for the overall population, the log-normal piecewise models produced a better fit compared to piecewise models using the exponential distribution. Piecewise models using a week 48 cut-off provided a reasonable fit to the observed data in both PD-L1 <1% and ≥1% subgroups. The week 96 cut-off piecewise models were not used as extrapolations at this later cut-off point were based on few patients in each of the subgroups.

To extrapolate PFS for nivolumab (PD-L1 <1% subgroup), the generalised gamma model was selected for extrapolation of PFS, providing good visual fit (and best statistical fit of non-spline models). The spline models provided better statistical fit than the standard parametric models, but the best fitting curves often produced logical inconsistencies when compared to the preferred extrapolation for OS. For the PD-L1 ≥1% subgroup, the log-logistic model provided the best statistical fit but a poor visual fit to the observed data. The one-spline hazards model provided reasonable statistical and visual fit, [redacted], and was thus selected for use in the model.

To extrapolate TTD for nivolumab (PD-L1 ≥1% subgroup), the two-spline normal model provided the best statistical fit. However, the one-spline odds model provided a better visual fit to the observed data compared to the one-spline odds model, [redacted], and was thus selected for use in the model.

Tables 4.2 and Table 4.3 provide an overview of the goodness-of-fit data for the patient subgroups based on PD-L1 <1% and ≥1%. Table 4.4 provides an overview of the company preferred approaches to estimate OS, PFS and TTD.

Table 4.2: Summary of goodness-of-fit data (PD-L1 <1% subgroup)

	OS		PFS		TTD	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Nivolumab						
Exponential	523.061	525.391	382.266	384.597	372.696	375.000
Weibull	521.397	526.058	370.017	374.678	367.723	372.331
Gamma	523.027	527.688	379.939	384.600	371.248	375.856
Gompertz	518.899	523.560	340.312	344.973	362.022	366.630
Log-normal	**514.495**	**519.157**	330.201	334.862	365.298	369.906
Log-logistic	517.230	521.892	317.282	321.944	357.779	**362.387**
Generalised-gamma	516.495	523.487	312.145	319.137	363.601	370.513
Spline models:						
1-Spline Hazard	517.110	524.103	303.342	310.334	361.395	368.307
2-Spline Hazard	516.808	526.131	304.969	314.292	359.192	368.408
1-Spline Odds	519.069	526.061	292.756	**299.748**	358.682	365.594
2-Spline Odds	517.343	526.666	**291.913**	301.236	357.682	366.898
1-Spline Normal	516.485	523.478	301.060	308.052	362.587	369.499
2-Spline Normal	517.139	526.462	517.139	526.462	**356.983**	366.200
IC						
Exponential	258.516	**260.204**	170.794	172.483	167.034	**168.698**
Weibull	260.161	263.539	168.161	171.538	167.801	171.128
Gamma	259.592	262.969	166.981	170.359	167.945	171.272
Gompertz	260.471	263.849	170.969	174.347	168.473	171.800
Log-normal	**257.796**	261.173	**166.113**	**169.491**	180.353	183.681
Log-logistic	258.502	261.880	167.172	170.550	171.449	174.776
Generalised-gamma	259.286	264.353	167.858	172.924	169.800	174.790
Spline models:						
1-Spline Hazard	259.223	264.289	167.859	172.925	169.608	174.598
2-Spline Hazard	261.034	267.789	169.768	176.524	167.844	174.498
1-Spline Odds	260.390	265.456	169.162	174.228	**166.443**	171.433
2-Spline Odds	261.636	268.391	170.964	177.719	168.035	174.689
1-Spline Normal	259.376	264.443	167.923	172.989	167.055	172.045
2-Spline Normal	261.335	268.091	169.906	176.662	169.906	176.560

Source: Based on CS Appendix B and the economic model
Note: the lowest AIC/BIC 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

Table 4.3: Summary of goodness-of-fit data (PD-L1 ≥1% subgroup)

	OS		PFS		TTD	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Nivolumab						
Exponential	645.037	647.601	397.867	400.344	544.974	547.538
Weibull	641.707	646.835	399.604	404.559	516.025	521.154
Gamma	644.015	649.144	398.397	403.352	522.798	527.927
Gompertz	635.344	640.473	398.474	403.428	513.679	518.808
Log-normal	637.062	642.191	388.003	392.957	519.720	524.849
Log-logistic	**634.880**	**640.009**	**387.144**	**392.098**	512.473	517.601
Generalised-gamma	637.890	645.583	389.960	397.392	514.839	522.532
Spline models:						
1-Spline Hazard	637.880	645.573	387.619	395.051	514.887	522.580
2-Spline Hazard	637.412	647.669	389.879	399.788	510.672	520.930
1-Spline Odds	636.398	644.091	387.811	395.243	509.638	**517.331**
2-Spline Odds	638.195	648.453	389.690	399.599	510.117	520.375
1-Spline Normal	637.380	645.073	389.888	397.320	511.956	519.649
2-Spline Normal	637.898	648.155	389.544	399.453	**509.520**	519.778
IC						
Exponential	352.238	354.349	223.310	225.421	188.395	190.438
Weibull	353.307	357.529	209.443	213.665	188.092	192.178
Gamma	351.796	356.018	**208.213**	**212.435**	189.581	193.667
Gompertz	354.055	358.277	216.230	220.452	**183.339**	**187.425**
Log-normal	**346.405**	**350.627**	211.391	215.612	210.804	214.890
Log-logistic	347.544	351.765	210.795	215.017	204.963	209.049
Generalised-gamma	348.282	354.615	210.183	216.516	184.181	190.310
Spline models:						
1-Spline Hazard	348.730	355.062	210.140	216.472	184.847	190.977
2-Spline Hazard	350.620	359.063	212.193	220.637	186.771	194.943
1-Spline Odds	349.279	355.612	211.530	217.863	191.835	197.964
2-Spline Odds	351.263	359.706	212.982	221.425	189.356	197.528
1-Spline Normal	348.181	354.513	210.215	216.547	203.170	209.300
2-Spline Normal	349.882	358.325	212.125	220.569	188.068	196.240

Source: CS Appendix B[13] and the economic model.
Note: the lowest AIC/BIC 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

Table 4.4: Summary selected parametric survival models

	Selected extrapolations		
	OS	**PFS**	**TTD**
Total population (original assessment; TA490)			
Nivolumab	Piecewise log-normal (different cut offs)[a]	Generalised gamma	Generalised gamma
IC	Piecewise log-normal (different cut offs)[a]	Generalised gamma	Generalised gamma
Total population (current assessment)			
Nivolumab	Piecewise log-normal 96-week cut off	Generalised gamma	2-spline normal
IC	Piecewise log-normal 96-week cut off	Generalised gamma	[redacted]
PD-L1 <1%			
Nivolumab	Piecewise log-normal 48-week cut off	Generalised gamma	[redacted]
IC	Kaplan-Meier data	Kaplan-Meier data	[redacted]
PD-L1 ≥1%			
Nivolumab	Piecewise log-normal 48-week cut off	1 spline hazards	1 spline odds
IC	Kaplan-Meier data	Kaplan-Meier data	[redacted]

Source: Company submission.[2]
IC = investigator's choice; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation
[a]The log-normal (had the best goodness-of-fit statistics) and log-logistic distributions were considered to be plausible candidates by the company

ERG comment: The main concerns of the ERG relate to: a) the generalisability of the IC arm to docetaxel; b) equivalence of nivolumab flat dose and weight-based nivolumab; c) treatment waning assumptions for OS; d) estimation of OS; e) use of fully parametric models and; f) estimation of TTD.

a) As stated in the ToE, docetaxel is the comparator of interest in the CDF review. Effectiveness of docetaxel was however informed by the IC arm from CheckMate 141. The IC arm consists of docetaxel, methotrexate and cetuximab. Therefore, the ERG (as also stated in the ERG report for TA490) would ideally prefer to use treatment specific effectiveness estimates in its base-case (i.e. using docetaxel specific data). Main reasons for this preference are 1) the potential impact on the relative treatment effect of nivolumab (see published subgroup analyses of CheckMate 141 indicating the relative treatment effect is for nivolumab is less in the docetaxel subgroup); 2) in the TA490 guidance, the committee noted these subgroup results and indicated that the committee was not persuaded by the company's assumption that docetaxel is equivalent to methotrexate (see also ToE) and; 3) given cetuximab which is not considered by clinical experts to be established practice in England (according to TA490 guidance). Therefore, the ERG requested (clarification question B1) that the company would use the subgroup of patients (from CheckMate 141) who were randomised to docetaxel versus. those who would be eligible to receive docetaxel according to IC, but who were randomised to nivolumab to inform the economic model. Unfortunately, the company did not provide these analyses.

b) As highlighted in Sections 2.2 and 4.1.3, it is unclear whether the nivolumab flat dose can be assumed equally effective to weight-based nivolumab and thus to what the degree the CheckMate 141 nivolumab (relative) effectiveness estimates are generalisable to the currently used nivolumab flat dose.
c) The company assumed no treatment waning of nivolumab effectiveness. However, the (smoothed) hazard rate of nivolumab and IC seem to converge (indicating similar mortality probabilities for both treatments, see clarification response Figure 2), this converging trend might potentially occur earlier if continued nivolumab treatment after two years was not allowed in the CheckMate 141 trial (i.e. if the two-year stopping rule for nivolumab was reflected in the clinical data). Therefore, the ERG include treatment waning of nivolumab OS benefit after year 5 (assuming similar mortality probabilities for both treatments after year 5).
d) In response to clarification question B2, the company provided different distributions (than Exponential and log-normal) to extrapolate OS using the piecewise model with a 96-week cut off. Based on the AIC (clarification response Table 10) the generalised gamma distribution seemed to be an appropriate candidate to extrapolate OS (given its lower AIC for IC). However, after inspection of the piecewise generalised gamma 96-week cut off curve, it seemed implausible for IC (given the mortality probability was 100% at a certain point). Therefore, the ERG would, based on the AIC, agree with the log-normal distribution to extrapolate OS using the piecewise model with a 96-week cut off. However, it should be noted that the selection of the approach to extrapolate OS is not informed by external validation (neither expert opinion nor external data) of the extrapolated OS. Hence, the plausibility of the extrapolated OS might be considered uncertain.
e) Although the committee clearly indicated that a piecewise model is expected to be used to extrapolate OS, the ERG agrees with the company that fully parametric models are still considered to provide plausible alternative to extrapolate OS. Therefore, it should be noted that the company explored fully parametric models to extrapolate OS in scenario analyses (CS Table 22), using log-normal and log-logistic distributions (both increasing the estimated ICERs).
f) The company used the two-spline normal (nivolumab) and the [redacted] (IC) to estimate TTD. The generalised gamma distribution was the preferred distribution to model TTD in TA490 and, according to the ERG, there is no clear justification to deviate from this. Additionally, [redacted]. Given the above, the ERG preferred to use the generalised gamma distribution to estimate TTD (for both nivolumab and IC) in the ERG base-case.

4.1.6 Adverse events

The approach to incorporate the impact of AEs on costs and utility was similar to TA490, i.e. 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. Additionally, pneumonitis was included based on ERG preferences.

ERG comment: 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.

4.1.7 Health-related quality of life

EQ-5D-3L data from the CheckMate 141 trial

In TA490, treatment-dependent health state utilities for the PF and PD states were derived from the EQ-5D-3L data collected from patients in the CheckMate 141 trial and analysed using mixed models in which progression status with and without treatment arm were included as covariates (see FAD Committee Papers 5; BMS additional evidence submitted in response to ACD; Appendix 1).[15] The company conducted no further analyses to estimate utility based on progression status. See Table 4.5 for the utility values used by the company (regression model 6; treatment dependent).

Table 4.5: Utility values estimated based on the CheckMate 141 trial (as per TA490)

	Nivolumab	IC	Difference
Regression model 6 (treatment dependent)			
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Regression model 7 (treatment independent)			
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

Source: CS and FAD Committee Papers 5. BMS additional evidence submitted in response to ACD, Appendix 1[15]
IC = investigator's choice; OS = overall survival

Duration of nivolumab quality-of-life benefit

According to the ToE for CDF review, the committee was concerned that the abovementioned utility values were associated with significant uncertainty and that quality-of-life benefit cannot be assumed to remain constant over time.

In the ToE it was stated that the most appropriate utility values lie between the treatment-dependent (regression model 6) and the treatment-independent (regression model 7) estimates. It is noteworthy that in one of the TA490 ERG addenda, the ERG explored the use of a disutility of [redacted] (difference in post progression utility between nivolumab and IC) for patients that discontinued nivolumab treatment as an alternative scenario (i.e. assuming treatment independent utility values after treatment discontinuation).[6] Also, in this addenda, the ERG wondered why the company did not opt to use regression Model 1 or Model 2 (adding a covariate for being off treatment), given the lower AIC. These models indicate the post-progression utility difference between the two treatments of [redacted] is potentially an overestimation given that this is [redacted] when considering the model with the lowest AIC.

To incorporate time dependency, the company used CheckMate 141 trial data to estimate utility decrements (both treatment-dependent and treatment-independent) related to time before death (CS Table 15). Using this approach utility decrements are applied for the proportion of patients who are predicted to die within the next three model cycles, with separate decrements applied based on whether patients are one (0–28 days), two (29–56 days) or three (57–84 days) cycles from death.

Adverse event utility decrements

Consistent with TA490, 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.

ERG comment: The main concerns of the ERG relate to: a) the health state utilities not being updated using the latest CheckMate141 data cut-off (15 October 2019); b) incorporating time dependency of nivolumab utility benefit.

a) In the ToE, the committee emphasised that it "was concerned that the utility values calculated by the company's mixed model approach were associated with significant uncertainty". In clarification question B7 the ERG requested the company to provide updated utilities based on progression status using the latest data from the CheckMate 141 trial (data cut-off: 15 October 2019). However, the company did not provide these. In response to clarification question B7 the company does state that "Whilst the number of observations has increased since the earlier data cut, there were very few additional observations in the IC arm ([redacted]) and at Week 57, [redacted] in the nivolumab arm were still in the study and able to complete an EQ-5D questionnaire.".[5] Although the ERG would have preferred updated utilities based on progression status, the ERG agrees with the company that the impact, given the limited number of additional observations, might be rather small.
b) In the ToE for CDF review NICE stated that it expected the quality-of-life benefit to not remain constant over time and that the appropriate utility values should be reviewed in light of any new evidence. The company tried to address this by applying decrements in utility based on the proportion of patients who are predicted to die within the next three model cycles (so last three months only). Whilst this approach may account, to some extent, for decreasing health state utilities over time (see CS Table 15), according to the ERG this does not address the committee's concerns regarding the nivolumab quality of life (treatment) over time. According to the ERG, it would have been more intuitive to use time since start/ stop treatment (rather than time to death) to address this concern. In the PD state patients in the nivolumab arm have a large treatment benefit compared to patients in the IC arm ([redacted] utility difference). As stated in the ERG report for TA490 (and highlighted above), the ERG wonders why the company did not opt to use a regression in which a covariate for being off treatment was added. This could then in turn be used for patients that discontinued nivolumab treatment (i.e. assuming treatment independent utility values after treatment discontinuation), as done in regression Model 1 or Model 2 (which had a better AIC than the currently used regression models). This would remove the constant quality of life benefit of treatment over time, which would have addressed the concerns highlighted in the ToE. Hence, to reflect the uncertainty, the ERG explored two base-cases, one with treatment-dependent utilities (based on regression model 6; Table 4.5), and one with treatment-independent utilities (based on regression model 7; Table 4.5). Additionally, the company's approach to obtain utility decrements related to time to death was not completely clear (e.g. what data cut-off was used, the number of observations included, details regarding the regression model), the ERG excluded the utility decrements related to time to death in scenario analyses.

4.1.8 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 of TA490.

Intervention and comparators' costs and resource use

Treatment costs

Drug acquisition costs were obtained from the British National Formulary for nivolumab and from the electronic market information tool for IC drugs. A PAS ([redacted]) has been agreed for nivolumab.

The dosing frequency for docetaxel, methotrexate and paclitaxel are provided in Table 4.6. Since the original submission for TA490, the licensed dose of nivolumab has been updated to a flat dose of 240 mg every two weeks, rather than the weight-based dose used in the CheckMate 141 trial (3 mg/kg every two weeks). The flat dose approximates the exposures achieved with 3 mg/kg in patients weighing 80 kg.

Table 4.6: Treatment costs

	Dosage	Treatment costs (per 28-day cycle)	Administration costs (per 28-day cycle) [b]	Monitoring costs (per 28-day cycle) [b]
Nivolumab (flat dose)	240 mg Q2W	[redacted]	£371.06	£190.79
Nivolumab (weight based)[a]	3 mg/kg Q2W	[redacted]	£371.06	£190.79
Docetaxel [a]	75 mg/m^2 Q3W	£33.32	£247.37	£190.79
Methotrexate [a]	40 mg/m^2 QW	£48.76	£742.12	£190.79
Paclitaxel [a]	80 mg/m^2 QW	£68.84	£742.12	£190.79

Source: CS and Economic model.[2]

[a]Mean weight and BSA were based on the population of European patients reported in CheckMate 141 ([redacted] respectively).

[b]All therapies included in the model are intravenously-administered and therefore assumed to incur the same administration costs per administration.

IC = investigator's choice; OS = overall survival

No vial sharing was assumed for all therapies. A reduction in dose intensity was included in the base-case based on the proportion of doses received that were delayed in CheckMate 141. 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, methotrexate or docetaxel – 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. The reduction in dose intensity calculated for docetaxel ([redacted]) was also applied to paclitaxel, in the absence of data for paclitaxel from CheckMate 141. Although the committee considered analyses without a stopping rule are more appropriate for decision-making (based on ToE), the company applied a two-year stopping rule.

Subsequent systemic therapy

In the base-case analysis, the proportion of patients who received subsequent systemic therapy post-discontinuation was assumed to be treatment independent, in line with ERG preferences (ERG report for TA490) and the ToE.

Health state and event costs

Health state and event costs were implemented as per TA490. Health state costs consisted of costs related to the PF and PD health states as well as event costs related to progression (one oncologist visit and one CT scan in order to confirm disease progression) and death (terminal care cost).

Adverse event costs

As per TA490, the costs per episode of treating AEs were sourced from currency codes for NHS reference costs and assumptions used in previous appraisals.

ERG comment: a) the validity of the TTD assumptions for UK clinical practice; b) incorporating dose intensity when calculating docetaxel treatment costs and; c) the two-year stopping rule.

- **a)** Compared with the CheckMate 141 trial, the SACT data provides real-world data that might better reflect UK clinical practice. To this extent, the ERG requested the company to provide a scenario analysis using the SACT data to estimate time to TTD for nivolumab (clarification question B6). In their response, the company stated that "TTD in the SACT cohort was generally higher than that observed in the CheckMate 141 trial, as shown in the company evidence submission. The use of TTD data from the SACT cohort in the cost-effectiveness analysis therefore produces a higher estimate of the ICER than the base-case analysis (i.e. using data from CheckMate 141) due to the increased costs related to treatment that are accrued in the nivolumab arm." The substantial increase in the ICER (+£14,198 compared to the CS base-case) highlights the importance of the TTD assumptions in the model and may be subject to a large degree of uncertainty. Hence, if the nivolumab treatment duration from the SACT is believed to better reflect UK clinical practice, this would substantially increase the estimated ICERs (both those presented as the ERG as well as CS base-case).
- **b)** In the calculation of treatments costs for docetaxel, when assuming no vial sharing, the company included the average dose intensity in their calculation of the number of required vials per mg/m2 group. As dose intensity is related to doses that are missed (rather than the number of vials per mg/m2 group), the dose intensity should rather be applied to the calculated docetaxel costs per administration. Hence, the ERG corrected the implementation of dose intensity, resulting in per cycle costs for docetaxel of £30.39 (instead of £33.32 per cycle; see Table 4.8).
- **c)** The company incorporated a two-year stopping rule to nivolumab. However, according to the ToE, the committee considered analyses without a stopping rule as more appropriate for decision-making. Moreover, excluding the two-year stopping rule is consistent with the CheckMate 141 trial data used to estimate effectiveness. The justification by the company to include the stopping rule is minimal (i.e. [redacted], and a two-year stopping rule has been shown to be clinically plausible during the CDF data collection period). Therefore, the ERG excluded the two-year stopping rule in its base-case

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company cost effectiveness results are described for the all-randomised population and patient subgroup based on PD-L1 status. First, the company stated that they have replicated the key cost effectiveness results (cost effectiveness (C-E) analysis 1) used in the committee's decision-making at the point of CDF entry (i.e. data cut-off: September 2016). Second, the company provided cost effectiveness results (C-E analysis 2) that incorporated data collected during the CDF data collection period (i.e. data cut-off: October 2019), which included the committee's preferred assumptions for decision-making at the point of CDF entry. Third, the company provided a revised base-case analysis C-E analysis 3). These cost effectiveness results incorporated data collected during the CDF data collection period, plus any associated changes to the company's preferred assumptions, as stated in Table 5.1. For the cost effectiveness analyses a flat dose of 240 mg every two weeks (Q2W) nivolumab was used.

Table 5.1: Key model assumptions and inputs

Model input and cross reference	C-E analysis 1 (Original assumptions)	C-E analysis 2	C-E analysis 3
OS, PFS and TTD data source	CheckMate 141 (Data cut-off: 20 September 2016)	CheckMate 141 (Data cut-off: 15 October 2019)	CheckMate 141 (Data cut-off: 15 October 2019)
OS extrapolation	Nivolumab and IC: piecewise with log-normal (20, 36 and 48 week cut-off points)	Nivolumab and IC: piecewise with log-normal (20, 36 and 48 week cut-off points)	Nivolumab and IC: piecewise with log-normal (96-week cut-off point)
Long-term treatment waning effect	Treatment waning at 5 years included	Treatment waning at 5 years included	Treatment waning at 5 years excluded
PFS extrapolation	Nivolumab and IC: generalised gamma	Nivolumab and IC: generalised gamma	No change
TTD extrapolation	Nivolumab and IC: generalised gamma	Nivolumab and IC: generalised gamma	Nivolumab: 2-spline normal IC: [redacted]
Utility values	**Treatment-specific** PF nivolumab: [redacted] PD nivolumab: [redacted] PF IC: [redacted] PD IC: [redacted] **Treatment independent** PF: [redacted] PD: [redacted]	**Treatment-specific** PF nivolumab: [redacted] PD nivolumab: [redacted] PF IC: [redacted] PD IC: [redacted] **Treatment independent** PF: [redacted] PD: [redacted]	**Treatment-specific** PF nivolumab: [redacted] PD nivolumab: [redacted] PF IC: [redacted] PD IC: [redacted] With time-to-death utility decrements applied

Model input and cross reference	C-E analysis 1 (Original assumptions)	C-E analysis 2	C-E analysis 3
Stopping rule	2-year stopping rule included	2-year stopping rule included	No change
ERG's amendments to the company's model	Adding the cost and disutility for pneumonitis and using treatment-independent proportions for subsequent treatment	Adding the cost and disutility for pneumonitis and using treatment-independent proportions for subsequent treatment	No change

Source: Based on CS Table 17.[2]
ACD: Appraisal Consultation Document; ERG: Evidence Review Group; FAD: Final Appraisal Determination; IC: investigator's choice; OS: overall survival; PD: progressed disease; PF: progression free; PFS: progression-free survival; TTD: time to treatment discontinuation

5.1.2 Overall population

Replication of the key cost effectiveness results used in committee's decision-making at the point of CDF entry

The company used a piecewise model using the log-normal distribution to model OS, extrapolated from 20, 36 and 48 weeks (estimated based on September 2016 data cut-off). The company used both treatment-dependent and treatment-independent utility values. The analyses include a PAS discount of [redacted]% to the list price of nivolumab. The ICER per QALY gained for nivolumab versus docetaxel ranged from £45,874 to £67,555 depending on the cut-off (20, 36, or 48 weeks) and utility (treatment-specific, or treatment independent) used (Table 5.2).

Table 5.2: Cost effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry (with PAS) – overall population, flat dose

Technologies	Incr. costs (£)	Incr. QALYs	ICER (£/QALY gained)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY gained)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY gained)
Piecewise log-normal cut-off point:	**20 weeks**			**36 weeks**			**48 weeks**		
Treatment-specific utility									
Docetaxel	[redacted]	[redacted]	£45,874	[redacted]	[redacted]	£41,304	[redacted]	[redacted]	£53,634
Paclitaxel	[redacted]	[redacted]	£42,252	[redacted]	[redacted]	£38,065	[redacted]	[redacted]	£49,363
Methotrexate	[redacted]	[redacted]	£43,215	[redacted]	[redacted]	£38,925	[redacted]	[redacted]	£50,498
Treatment-independent utility									
Docetaxel	[redacted]	[redacted]	£58,448	[redacted]	[redacted]	£52,528	[redacted]	[redacted]	£67,555
Paclitaxel	[redacted]	[redacted]	£53,833	[redacted]	[redacted]	£48,409	[redacted]	[redacted]	£62,175
Methotrexate	[redacted]	[redacted]	£55,059	[redacted]	[redacted]	£49,503	[redacted]	[redacted]	£63,604

Source: Based on CS Table 17.[2]

CS = company submission; ICER = incremental cost effectiveness ratio; LY = life-years; PAS = Patient Access Scheme; QALYs = quality-adjusted life years; incr. = incremental

ERG comment: As stipulated in the ToE, the company should provide a replication of the key cost effectiveness results used in the committee's decision-making at the point of CDF entry. The ICERs abovementioned results (reported in CS Table 17 and Appendix D Table 15) do not appear to be in line with the ICERs reported in the Final Appraisal Document or ToE for nivolumab compared with docetaxel (i.e. these ICERs do not range between either £45,000 and £73,600 or, as per the commercial access agreement, £30,377 and £49,408 per quality-adjusted life year gained). After clarification (response to question B12) from the company, it became clear that the differences were due the application of the higher [redacted]% PAS discount and/ or the application of the two-year stopping rule. Based on these clarifications, the ERG was able to reproduce the ICER used in the committee's decision-making at the point of CDF entry.

Cost effectiveness results that incorporate data collected during the CDF data collection period, with the assumptions used in committee's decision-making at the point of CDF entry

The company used a piecewise model using the log-normal distribution to model OS, extrapolated from 20, 36 and 48 weeks. The company used both treatment-dependent and treatment-independent utility values. The analyses included a PAS discount of [redacted]% to the list price of nivolumab. The ICER per QALY gained for nivolumab versus docetaxel ranged from £41,906 to £55,051 depending on the cut-off (20, 36, or 48 weeks) and utility (treatment-specific, or treatment independent) used (Table 5.3).

Table 5.3: Cost effectiveness analysis 2: Analysis that demonstrated plausible potential for cost effectiveness at CDF entry – incorporating updated clinical evidence (with PAS) – overall population, flat dose

Technologies	Incr. costs (£)	Incr. QALYs	ICER (£/QALY gained)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY gained)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY gained)
Piecewise log-normal cut-off point:	**20 weeks**			**36 weeks**			**48 weeks**		
Treatment-specific utility									
Docetaxel	[redacted]	[redacted]	£43,959	[redacted]	[redacted]	£41,906	[redacted]	[redacted]	£45,793
Paclitaxel	[redacted]	[redacted]	£40,644	[redacted]	[redacted]	£38,757	[redacted]	[redacted]	£42,333
Methotrexate	[redacted]	[redacted]	£41,527	[redacted]	[redacted]	£39,596	[redacted]	[redacted]	£43,255
Docetaxel	[redacted]	[redacted]	£53,510	[redacted]	[redacted]	£50,728	[redacted]	[redacted]	£55,051
Paclitaxel	[redacted]	[redacted]	£49,474	[redacted]	[redacted]	£46,916	[redacted]	[redacted]	£50,892
Methotrexate	[redacted]	[redacted]	£50,550	[redacted]	[redacted]	£47,932	[redacted]	[redacted]	£52,000

Source: Based on CS Table 18.[2]

CS = company submission; ICER = incremental cost effectiveness ratio; LY = life-years; PAS = Patient Access Scheme; QALYs = quality-adjusted life years; incr. = incremental

ERG comment: As stipulated in the ToE, the company should provide a replication of the key cost effectiveness results that incorporate data collected during the CDF data collection period, with the assumptions used in committee's decision making at the point of CDF entry. Because the results of the replication (cost effectiveness analysis 1) was not consistent with the original results (section above), the validity of the results (cost effectiveness analysis 2) was unclear. However, the ERG was able to replicate the original results after clarification of the company (section above). Therefore, the ERG considers the results of cost effectiveness analysis 2 to be reproducible (using the cost effectiveness estimates at CDF entry as starting point).

Cost effectiveness results that incorporate data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions.

The analyses included a PAS discount of [redacted]% to the list price of nivolumab. The increased QALYs and costs for nivolumab resulted in ICERs of £37,236, £34,186, and £35,019 per QALY gained versus docetaxel, paclitaxel and methotrexate, respectively (Table 5.4).

Table 5.4: New company base-case results (nivolumab with PAS) – overall population

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Nivolumab	[redacted]	1.31	[redacted]				
Docetaxel	£10,569	0.67	0.35	[redacted]	0.65	[redacted]	£37,236
Paclitaxel	£12,000	0.67	0.35	[redacted]	0.65	[redacted]	£34,186
Methotrexate	£11,609	0.67	0.35	[redacted]	0.65	[redacted]	£35,019

Source: Based on CS Table 19.[2]
CS = company submission; ICER = incremental cost effectiveness ratio; LY = life-years; PAS = Patient Access Scheme; QALYs = quality-adjusted life years

ERG comment: It is noteworthy that in the CS base-case the majority of the estimated QALY gain (~65%) is attributable to the period after disease progression has been confirmed. This implies that additional benefit continues to accrue to patients whose disease has progressed. The plausibility of the proportion of post-progression gains is unclear to the ERG.

5.1.3 Patients with PD-L1 <1% and ≥1%

As requested in the ToE, the company provided cost-effectiveness results of nivolumab versus docetaxel for the PD-L1 expression subgroups (PD-L1<1%, and PD-L1≥1%) (Table 5.5). The results for the revised base-case (cost effectiveness analysis 3) incorporate the inputs and assumptions as described in Table 5.L1.

According to the company, the clinical effectiveness results by PD-L1 status could not demonstrate a statistically significant difference between the subgroups in the treatment effect on OS. Therefore, the company stated that the evidence is such that the overall population should be considered as the patient population within the CDF review.

The revised base-case analyses (cost effectiveness analysis 3) (Table 5.5) resulted in ICERs of £46,309 and £36,163 per QALY gained for the subgroups PD-L1<1% and PD-L1≥1%, respectively.

Table 5.5: Summary of cost effectiveness analyses and revised base-case (with PAS) versus docetaxel only – PD-L1 subgroups, flat dose.

Analysis		ICER (£/QALY gained) versus docetaxel	
Utility values		**Treatment-specific**	**Treatment-independent**
PD-L1 <1%			
Cost effectiveness analysis 1, flat dose			
Piecewise log-normal cut-off point	20 weeks	£39,218	£53,242
	36 weeks[a]	-	-
	48 weeks	£65,154	£102,195
Cost effectiveness analysis 2, flat dose			
Piecewise log-normal cut-off point	20 weeks	£42,558	£54,341
	36 weeks[a]	-	-
	48 weeks	£47,982	£61,729
Cost effectiveness analysis 3, flat dose		£46,309	-
PD-L1 ≥1%			
Cost effectiveness analysis 1, flat dose			
Piecewise log-normal cut-off point	20 weeks	£43,647	£51,809
	36 weeks	£35,882	£41,020
	48 weeks	£41,581	£47,714
Cost effectiveness analysis 2, flat dose			
Piecewise log-normal cut-off point	20 weeks	£42,945	£49,710
	36 weeks	£42,061	£48,051
	48 weeks	£44,045	£50,253
Cost effectiveness analysis 3, flat dose		£36,163	-

Source: Based on CS Table 20.2

aAs noted in FAD Committee Papers 8; appendix, with 2-year stopping rule, the extrapolation of OS using the piecewise model with the 36-week cut-off point was not considered plausible by the company, particularly for the PD-L1 <1% subgroup. This cut-off point creates a kink in the shape of the survival curve for IC which causes the IC curve to cross the nivolumab curve and produce a plateau after 3 years. The resulting survival curve is therefore wholly clinically implausible given the known prognosis for patients with R/M SCCHN after platinum therapy. ICERs have therefore not been presented from the PD-L1 <1% subgroup using the 36-week cut-off point.

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: Patient Access Scheme; PD-L1: programmed death ligand 1; QALYs, quality-adjusted life years; R/M SCCHN: recurrent/metastatic squamous cell carcinoma of the head and neck.

ERG comment: According to Table 13 of the CS, the PD-L1 score for patients was not recorded for 42% (n=210) of the SACT data cohort study population. The ERG is concerned that testing for PD-L1 expression is not part of usual care for treating SCCHN patients within the UK. This would mean that if nivolumab would only be accepted for treating patients according to their PD-L1 expression level, additional testing on PD-L1 expression would be required, which will lead to additional costs related to

nivolumab. However, in response to clarification question B10, the company argues that PD-L1 testing is standard clinical practice in the UK, when required.

5.2. Company's sensitivity analyses

The company presented probabilistic sensitivity analysis (PSA), deterministic sensitivity analysis (DSA) and deterministic scenario analysis.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) with 1,000 iterations was conducted. In each iteration, the model inputs were randomly drawn from the specified distributions. Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a particular value, it was varied by ±15%.

The base-case results using PSA are presented in Table 5.6 and resulted in slightly lower ICERs than those presented for the new deterministic company base-case. The ICERs were £36,255, £33,340 and £34,059 for nivolumab versus docetaxel, paclitaxel and methotrexate, respectively.

Table 5.6: Revised base-case results (average probabilistic) (with PAS) – overall population, flat dose

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,574	0.36	[redacted]	[redacted]	£36,255
Paclitaxel	£11,983	0.36	[redacted]	[redacted]	£33,340
Methotrexate	£11,638	0.36	[redacted]	[redacted]	£34,059

Source: Based on CS Table 21.[2]
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 18 and 19). The company reported a [redacted] 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 in the model. Whenever available, values were varied using the standard error obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a particular value, it was varied by ±20%.

The DSA results are presented using tornado diagrams with the top 10 drivers of cost effectiveness in CS Figure 20. The company identified the following parameters as the main influential parameters on the cost effectiveness (in order of importance):

1. Nivolumab treatment frequency
2. Nivolumab utility value – Progressed disease
3. Nivolumab utility value – Progression free
4. Comparator utility value – Progressed disease
5. Comparator utility value – Progression free

6. Nivolumab administration cost
7. Nivolumab monitoring cost
8. Docetaxel administration cost
9. Docetaxel monitoring cost
10. Docetaxel treatment frequency

Deterministic scenario analysis

The company performed various deterministic scenario analyses, see Table 5.7.

Table 5.7: Deterministic scenario analyses performed by the company – overall population, flat dose

Scenario		Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on base-case ICER
	Base-case		£37,236	-
1	Alternative OS assumption	Piecewise log-normal 48-week cut-off for OS extrapolation	£40,167	+£2,931
2	Alternative OS assumption	Fully parametric log-normal	£41,158	+£3,922
3	Alternative OS assumption	Fully parametric log-logistic	£38,896	+£1,660
4	Treatment-dependent utility values	Treatment-dependent utility values No time-to-death utility decrements	£35,340	-£1,896
5	Treatment-independent utilities	Treatment-independent utility values Time-to-death utility decrements	£41,418	+£4,182
6	Treatment-independent utilities	Treatment-independent utility values No time-to-death utility decrements	£41,537	+£4,301
7	No stopping rule	2-year stopping rule is not applied	£49,018	+£11,782
8	Treatment waning (5 years)	Treatment waning applied from 5 years	£45,014	+£7,778
9	Treatment waning (7 years)	Treatment waning applied from 7 years	£41,639	+£4,403
10	Treatment waning (10 years)	Treatment waning applied from 10 years	£39,214	+£1,978
11	"Partial" treatment waning (5 years)	Treatment waning applied from 5 years for [redacted]% of patients only	£41,821	+£4,585
12	"Partial" treatment waning (7 years)	Treatment waning applied from 7 years for [redacted]% of patients only	£39,921	+£2,685
13	"Partial" treatment waning (10 years)	Treatment waning applied from 10 years for [redacted]% of patients only	£38,472	+£1,237

Source: Based on CS Table 22.[2]
Abbreviations: ICER: incremental cost effectiveness ratio; OS: overall survival.

The results of the scenario analyses are summarised in Table 5.7, showing that alternative OS assumptions, stopping rule, treatment-independent utilities, and treatment waning effects had a strong impact on the base-case ICER. The most influential scenarios were 1) removing the two-year stopping

rule (scenario 7; impact on base-case ICER: +£11,782), 2) implementing treatment waning from five years (scenario 8; base-case ICER: +£7,778), and 3) implementing partial treatment waning from five years (scenario 11; base-case ICER: +£4,585)

ERG comment: In addition to the sensitivity analyses provided in the CS (based on "cost effectiveness analysis 3", revised company base-case). The company also provided sensitivity analyses for "cost effectiveness analysis 2" (updated committee preferred base-case) in response to clarification question B13.

5.3 Model validation and face validity check

The company did not report on the validity of the economic model.

ERG comment: The ERG was able to reproduce the results mentioned in ToE (the committee preferred ICER range £45,000 and £73,600 per QALY per QALY gained). Moreover, the changes implemented related to updating of input parameters and not to the model structure. Therefore, the ERG believes that the internal validation described in TA490 (detecting no major errors) is still valid. However, also the ERG's concerns in TA490 regarding the lack of external validation hampers the interpretation of the cost effectiveness.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations from Chapter 4, the ERG defined a new base-case. This base-case included multiple adjustments to the company base-case presented in the CS. These adjustments mainly consisted of adjustments that could be categorised as matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred):

1. Include treatment waning of nivolumab OS benefit after year 5
   The (smoothed) hazard rate of nivolumab and IC seem to converge (indicating similar mortality probabilities for both treatments), this converging trend might potentially occur earlier if continued nivolumab treatment after two years was not allowed in the CheckMate 141 trial (i.e. if the two-year stopping rule for nivolumab was reflected in the clinical data) (Section 4.1.5).
2. Using the generalised gamma model for estimating TTD
   The generalised gamma distribution was the preferred distribution to model TTD in TA490 and, according to the ERG, there is no clear justification to deviate from this. Additionally [redacted]
   (Section 4.1.5).
3. Include both treatment dependent and treatment independent utility
   Although the company attempted to incorporate time dependent utility values, the time to death utility are more likely to reflect the declining utility towards the end of life than reflecting a nivolumab quality-of-life benefit that is not constant over time (Section 4.1.7).
4. Excluding the two-year stopping rule
   According to the ToE, the committee considered analyses without a stopping rule are more appropriate for decision-making. Moreover, excluding the two-year stopping rule is consistent with the CheckMate 141 trial data used to estimate effectiveness. The justification by the company to include the stopping rule is minimal (i.e. [redacted]*, and a two-year stopping rule has been shown to be clinically plausible during the CDF data collection period).*
5. Correcting error related to implementation of docetaxel dose intensity
   The ERG corrected an error related to the implementation of dose intensity for calculating docetaxel treatment costs (Section 4.1.8).

In addition, the following scenario analyses were performed:

1. Excluding the estimated utility decrements related to time before death

For the PD-L1 subgroups the following adjustments were implemented:

1. Using the piecewise log-normal 48-week cut off for estimating OS (i.e. [redacted]).
2. Using the generalised gamma model for estimating PFS (i.e. [redacted]).
3. Using the one-spline normal and generalised gamma models for estimating TTD for the PD-L1 <1% and PD-L1 ≥1% subgroups respectively (i.e. [redacted]).

These distributions were selected given the reasonable AIC and since these did not produce logical inconsistencies between TTD and OS.

For all three adjustments, [redacted].

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Correcting the docetaxel dose intensity error as well as excluding the estimated utility decrements related to time before death (while assuming treatment dependent utility) have a minor impact on the estimated ICER. The other adjustments have a more pronounced impact on the estimated ICER (Tables 6.1-6.5).

6.3 ERG's preferred assumptions

Table 6.1: ERG analyses (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
Company base-case					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.35	[redacted]	[redacted]	£37,236
1 Company base-case + OS treatment waning[a]					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.35	[redacted]	[redacted]	£45,017
2 Company base-case + generalised gamma model for estimating TTD					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,505	0.35	[redacted]	[redacted]	£39,959
3 Company base-case + treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.38	[redacted]	[redacted]	£41,418
4 Company base-case + excluding the 2-year stopping rule					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.35	[redacted]	[redacted]	£49,018
5 Company base-case + correcting error related to implementation of docetaxel dose intensity					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,561	0.35	[redacted]	[redacted]	£37,254

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1 Company base-case + OS treatment waning + generalised gamma model for estimating TTD + excluding the 2-year stopping rule					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.35	[redacted]	[redacted]	£53,485
7 ERG base-case 2 Company base-case + OS treatment waning + generalised gamma model for estimating TTD + excluding the 2-year stopping rule + treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.38	[redacted]	[redacted]	£60,094

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation
[a]A minimum function was implemented to prevent that PFS would exceed OS (implemented in cells 'Nivolumab Traces'!G11:G370 and 'Docetaxel Traces'!G11:G370)
[b]The following cells were adjusted: Settings!J72:N72, 'Treatment Costs'!N24 and 'Docetaxel Traces'!AU11:AU369

Table 6.2: ERG scenario (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility + excluding the estimated utility decrements related to time before death					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.36	[redacted]	[redacted]	£50,140
7 ERG base-case 2 - treatment independent utility + excluding the estimated utility decrements related to time before death					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.40	[redacted]	[redacted]	£60,264

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

Table 6.3: ERG base-case (probabilistic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility[a]					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,556	0.36	[redacted]	[redacted]	£54,348

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
7 ERG base-case 2 - treatment independent utility[a]					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,511	0.38	[redacted]	[redacted]	£61,293

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

[a]The PSA produced 1 to 2 errors (#VALUE), these simulations were ignored to calculate the probabilistic means.

Table 6.4: ERG base-case; PD-L1 <1% subgroup (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,048	0.41	[redacted]	[redacted]	£53,152
7 ERG base-case 2 - treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,048	0.43	[redacted]	[redacted]	£62,895

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

Table 6.5: ERG base case; PD-L1 ≥1% subgroup (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£9,981	0.29	[redacted]	[redacted]	£54,362
7 ERG base-case 2 - treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£9,981	0.31	[redacted]	[redacted]	£58,926

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

6.4 Conclusions of the cost effectiveness section

The company base-case ICER (probabilistic) of nivolumab (with PAS) compared with docetaxel was £36,255 per QALY gained. The ERG has incorporated various adjustments to the company base-case. The ERG base-case resulted in an ICER range (probabilistic) of £54,348 to £61,293 per QALY gained for nivolumab (with PAS) versus docetaxel. 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 states; 3) including treatment waning of nivolumab OS benefit after year 5 and; 4) excluding the two-year stopping rule. Additionally, the company explored using SACT data to estimate TTD (i.e. nivolumab treatment duration) in scenario analyses. Compared with the CheckMate 141 trial, the SACT data provides real-world data that might better reflect UK

clinical practice. The higher TTD observed in the SACT data resulted in a substantially increased ICER (+£14,198 compared to the CS base-case) highlighting the importance of the TTD assumptions in the model.

The equivalence assumptions between docetaxel and methotrexate as well as between the nivolumab flat dose and weight-based nivolumab can be questioned. Unfortunately, the company did not provide analyses based on the docetaxel subgroup (requested during the clarification phase), nor evidence to support the equivalence assumption for nivolumab (flat dose versus weight-based). An additional area of uncertainty is the extrapolation of the nivolumab quality-of-life benefit over time. Although the company implemented utility decrements related to the time to death, the ERG believes that the committee's concern (i.e. emphasizing that quality-of-life benefit cannot be assumed to remain constant over time) is not appropriately addressed. Therefore, the ERG base-case is presented as a range conditional on treatment dependent and treatment independent utilities to address the uncertainty related to the nivolumab utility benefit over time.

The subgroup analyses (based on PD-L1 status) performed by the ERG resulted in ICERs that ranged between £53,152 and £62,895 per QALY gained. It should however be noted that these subgroup analyses did not incorporate any additional costs related to PD-L1 which would be required if PD-L1 testing is not part of UK clinical practice.

In conclusion, the ERG base-case ICERs are estimated to be in the range between £54,348 and £61,293 per QALY gained, reflecting the uncertainty related to nivolumab quality-of-life benefits over time. Uncertainty that was not captured in this range included the equivalence assumptions between docetaxel and methotrexate as well as between the nivolumab flat dose and weight-based nivolumab. Additionally, if the nivolumab treatment duration from the SACT is believed to better reflect UK clinical practice (than TTD from CheckMate 141), this would substantially increase the estimated ICERs.

7. END OF LIFE

The ToE stated that nivolumab meets the end-of-life criteria, i.e. "*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*".[1, 16] The ERG can confirm that there is no change in OS, however measured, that would suggest that they are not still fulfilled.

8. REFERENCES

[1] National Institute for Health and Care Excellence. *Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (TA490): terms of engagement for CDF review*. London: National Institute for Health and Care Excellence, 2018

[2] Bristol-Myers Squibb Pharmaceuticals Ltd. *Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (CDF review of TA490) [ID1585]. Cancer Drugs Fund Review of TA490. Company evidence submission for committee*: Bristol-Myers Squibb Pharmaceuticals Ltd., 2020

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy (CDF Review of TA4900 [ID1585]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Thursday 9 April 2020** using the below 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 committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Section 1: Major Comments

Issue 1 Description of the patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12, 14, 19, 22 (Table 2.1) and 45: *"adults with recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN) that progressed within six months of platinum-based therapy,* ***in either the early or locally advanced disease stage****"*	The ERG have reported the population as specified in the Terms of Engagement document accurately, but BMS believe this to be an inaccuracy within the Terms of Engagement document itself. The patient population should always be stated as "*adults with recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN) that progressed within six months of platinum-based therapy"* only.	The inclusion of the phrase "*in either the early or locally advanced disease stage"* is not in line with the licence for this indication, nor does it reflect the patient population for whom NICE originally recommended this treatment for use within the Cancer Drugs Fund. The licence, trial eligibility criteria and the original recommendation from NICE are consistent with one another insofar as they do not specify the setting in which patients progressed (thus progression could occur in the R/M setting, as well as the early or locally advanced disease setting). Therefore, inclusion of this phrase does not represent the licensed population, nor the population who receive nivolumab in clinical practice in the Cancer Drugs Fund, and thus should have not been included in the Terms of Engagement document.	This is not a factual inaccuracy since this is what the ToE stated. The company are right that there is an apparent discrepancy and the ERG have highlighted this under Assumption 1 of the ToE for the committee to consider.

Issue 2 Consideration of comparators in the Terms of Engagement document.

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 12: *"Using the all-randomised data, including that from the whole IC arm implies equivalence between docetaxel and methotrexate,* ***which the ToE explicitly rejects****"*	This statement from the ERG does not accurately reflect what was presented in the Terms of Engagement document, and thus should be amended as follows: "Using the all-randomised data, including that from the whole IC arm implies equivalence between docetaxel and methotrexate, **which, as reported in the ToE, was an assumption that the committee were not persuaded by in TA490**".	The Terms of Engagement document states that *"the committee were not persuaded by the company's assumption that docetaxel is equivalent to methotrexate",* it does not explicitly reject this assumption.	Not a factual inaccuracy.

Issue 3 Equivalence between the flat dose and the weight-based dose of nivolumab

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 77. *"Unfortunately, the company did not provide analyses based on the docetaxel subgroup (requested during the clarification phase), nor evidence to support the equivalence assumption for nivolumab (flat dose versus weight-based)"*	The ERG's statement is misleading, since the company provided justification for the equivalence assumption between the flat dose and weight-based dose of nivolumab in the form of the EMA's acceptance of the change in the licensed dose. *"Unfortunately, the company did not provide analyses based on the docetaxel subgroup (requested during the clarification phase), nor evidence to support the equivalence assumption for nivolumab (flat dose versus weight-based).* ***The equivalence assumption between the flat dose and weight-based dose of nivolumab has however been accepted by the EMA, as described in the***	Justification for the equivalence assumption between the flat dose and weight-based dose of nivolumab was provided in the response to the clarification questions. The acceptance of this equivalence assumption by the EMA is an important consideration that should be included in the ERG's conclusions.	Not a factual inaccuracy.

	company's response to the clarification questions*"*		

Issue 4 Inaccurate reporting from the clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 37. *"The company response to clarification showed that there was weak evidence of an interaction (p=0.077) indicating that the treatment effect of nivolumab* ***differed*** *between the groups based on PD-L1 status, although the HRs were not reported"*	BMS believe this statement is misleading and should be amended as follows: "The company response to clarification showed that there was weak evidence of an interaction (p=0.077) indicating that the treatment effect of nivolumab **may differ** between the groups based on PD-L1 status, although the HRs were not reported."	The evidence for an interaction (p=0.077) is not statistically significant at the 5% significance level, so it should not be stated that this evidence indicates the treatment effect of nivolumab differed between the groups based on PD-L1 status.	Not a factual inaccuracy.

Issue 5 Omission of relevant context regarding stopping rule

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 62 and Page 73. *"The justification by the company to include the stopping rule is minimal (i.e.* [redacted]*, and a two-year stopping rule has been shown to be clinically plausible during the CDF data collection period)"*	The discussion should be amended to also note that the use of a stopping rule was considered to be acceptable by clinicians consulted as part of the original appraisal (FAD Committee Papers 2 and 3; Comments on the ACD) and also NHS England (ACD Committee Papers 5; NHS England statement).	The ERG's statement should include the full justification for the stopping rule that was provided in the company submission in Table 16.	Not a factual inaccuracy.

Section 2: Other Comments

Issue 6 Misreporting from the submission

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 33. Table 3.4 The 95% confidence interval for CheckMate 141, nivolumab arm, 18-month survival rate is incorrect. The ERG reports *"**21.5 (16.2, 27.3)**"*	The data should be amended to "**21.5 (16.2, 27.4)**".	Accurate reporting of the overall survival data from CheckMate 141.	Corrected.

Issue 7 Missing text

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 40. *"The company also noted that at six months 28% of SACT patients were still receiving treatment as opposed to [redacted] of the CheckMate 141 patients and at 12 months 17% of patients in the SACT database"*	The sentence is incomplete (and missing confidentiality highlighting), and should be amended as follows: *"The company also noted that at six months 28% of SACT patients were still receiving treatment as opposed to [redacted]% of the CheckMate 141 patients and at twelve months 17% of patients in the SACT database were still receiving treatment as opposed to [redacted]% of the CheckMate 141 patients."*	Typographical error and missing commercial in confidence highlighting.	Corrected.

Issue 8 Misreporting from the SACT report

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 41. Table 3.8 For the SACT data, the number of events is inaccurately reported as *"**506/506**".*	The data should be amended to **"394/506"**.	Accurate reporting of the SACT time to treatment discontinuation data.	Corrected.

Issue 9 Misreporting from the clarification questions

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>KSR response</th></tr>
<tr>
<td>Page 44. Table 3.10
The adverse event data from the original data cut of CheckMate 141 is inaccurately reported for the original data cut (please see below):
<table>
<tr><th rowspan="2">Adverse event, n (%)</th><th colspan="2">Nivolumab (n=236)</th><th colspan="2">IC (n=111)</th></tr>
<tr><th>Any grade</th><th>Grade 3-4</th><th>Any grade</th><th>Grade 3-4</th></tr>
<tr><td>All causality AEs</td><td>232 (98.3)</td><td>117 (49.6)</td><td>109 (98.2)</td><td>70 (63.1)</td></tr>
<tr><td>Drug-related AEs</td><td>146 (61.9)</td><td>37 (15.7)</td><td>88 (79.3)</td><td>41 (36.9)</td></tr>
</table>
</td>
<td>This data should be amended as shown below. BMS also recommend including labels in the table headings for the different data cuts.
<table>
<tr><th rowspan="2">Adverse event, n (%)</th><th colspan="2">Nivolumab (n=236)</th><th colspan="2">IC (n=111)</th></tr>
<tr><th>Any grade</th><th>Grade 3-4</th><th>Any grade</th><th>Grade 3-4</th></tr>
<tr><td>All causality AEs</td><td>232 (98.3)</td><td>113 (47.9)</td><td>109 (98.2)</td><td>69 (62.2)</td></tr>
<tr><td>Drug-related AEs</td><td>146 (61.9)</td><td>36 (15.3)</td><td>88 (79.3)</td><td>40 (36.0)</td></tr>
</table>
</td>
<td>Accurate reporting of the adverse event data from the original data cut of CheckMate 141.</td>
<td>Corrected.</td>
</tr>
</table>

Section 3: Confidentiality highlighting amendments

Issue 10 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 14 and 44. “[redacted]”	CIC confidentiality highlighting should be added to this sentence. “[redacted]”	This sentence describes time to treatment discontinuation data, and is therefore commercially sensitive.	Changed, including the sentence on page 44: *“The PD-L1 ≥ 1% group receiving nivolumab had a longer median TTD than those receiving IC but the median TTD was the same in each group in those patients with PD-L1 < 1%.”*

Issue 11 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 44. *“However, [redacted], the median TTD was shorter than in the SACT data (three months)”*	CIC confidentiality highlighting should be added to this sentence. *“However, [redacted], the median TTD was shorter than in the SACT data (three months)”*	This sentence describes time to treatment discontinuation data, and is therefore commercially sensitive.	Changed.

Section 4: Issues relating to the amendments made by the ERG to the model

Issue 12 Change to the modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	KSR response
Page 62. *"In the calculation of treatments costs for docetaxel, when assuming no vial sharing, the company included the average dose intensity in their calculation of the number of required vials per mg/m2 group. As dose intensity is related to doses that are missed (rather than the number of vials per mg/m2 group), the dose intensity should rather be applied to the calculated docetaxel costs per administration. Hence, the ERG corrected the implementation of dose intensity, resulting in per cycle costs for docetaxel of £30.39 (instead of £33.32 per cycle; see Table 4.8)."*	BMS agree with the ERG's correction, but suggest the following amendments: • Dose intensity should first be removed from all vial calculations for all treatments ("Treatment Costs" sheet, I and J columns of all groups. e.g. Group 1: I31–J35). • Then, instead of applying dose intensity directly to the traces (e.g. column AU of the docetaxel trace), dose intensity should then be applied to the weighted average acquisition costs of all treatments ("Treatment Costs" sheet, H106, K106–M106) • The weighted average acquisition costs inform the acquisition costs per cycle ("Treatment Costs" sheet, H261–264) which are then used to calculate the average cost per patient on subsequent therapy ("Treatment Costs" sheet H286–K286) • Thus, this approach accounts for reduced dose intensity/missed doses when docetaxel (and other comparators) are given as subsequent therapies The results of the ERG's additional analyses	The ERG's correction does not account for reduced dose intensity/missed doses when docetaxel (and other comparators) are given as subsequent therapies. The cost of subsequent therapies might therefore also be overestimated in the model, which would affect the results of the analysis versus docetaxel (given that patients are assumed to receive methotrexate as a subsequent therapy following docetaxel).	Not a factual inaccuracy: rather proposed further adjustments .The company agrees with the ERG's correction and proposes further adjustments related to the costs of subsequent therapies in the economic model. Moreover, the proposed further adjustments have a negligible impact on the estimated ICER (resulting in an ICER difference ranging between £2-£5).

	(deterministic only) (Tables 6.1, 6.2, 6.4 and 6.5) incorporating this change to modelling dose intensity have been presented in Appendix 1.		

Appendix 1: Evidence Review Group's additional analyses incorporating the correction to implementation of dose intensity

Table 6.1: ERG analyses (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
Company base-case					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.35	[redacted]	[redacted]	£37,236
1 Company base-case + OS treatment waning[a]					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.35	[redacted]	[redacted]	£45,017
2 Company base-case + generalised gamma model for estimating TTD					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,505	0.35	[redacted]	[redacted]	£39,959
3 Company base-case + treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.38	[redacted]	[redacted]	£41,418
4 Company base-case + excluding the 2-year stopping rule					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,569	0.35	[redacted]	[redacted]	£49,018
5 Company base-case + correcting error related to implementation of docetaxel dose intensity					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£ 10,555	0.353	[redacted]	[redacted]	£ 37,257
6 ERG base-case 1 Company base-case + OS treatment waning + generalised gamma model for estimating TTD + excluding the 2-year stopping rule					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,492	0.353	[redacted]	[redacted]	£ 53,488
7 ERG base-case 2 Company base-case + OS treatment waning + generalised gamma model for estimating TTD + excluding the 2-year stopping rule + treatment independent utility					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,492	0.377	[redacted]	[redacted]	£ 60,098

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

[a]A minimum function was implemented to prevent that PFS would exceed OS (implemented in cells 'Nivolumab Traces'!G11:G370 and 'Docetaxel Traces'!G11:G370)

[b]The following cells were adjusted: Settings!J72:N72, 'Treatment Costs'!N24 and 'Docetaxel Traces'!AU11:AU369

Company base case and ERG analyses 1–4 have remained unchanged.

Table 6.2: ERG scenario (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility + excluding the estimated utility decrements related to time before death					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,492	0.359	[redacted]	[redacted]	£ 50,143
7 ERG base-case 2 - treatment independent utility + excluding the estimated utility decrements related to time before death					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,492	0.401	[redacted]	[redacted]	£ 60,268

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

Table 6.3: ERG base-case; PD-L1 <1% subgroup (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,043	0.405	[redacted]	[redacted]	£53,157
7 ERG base-case 2 - treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,043	0.433	[redacted]	[redacted]	£62,900

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

Table 6.4: ERG base case; PD-L1 ≥1% subgroup (deterministic), nivolumab with PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
6 ERG base-case 1- treatment dependent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£9,976	0.291	[redacted]	[redacted]	£54,364

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Nivolumab ICER (£/QALY)
7 ERG base-case 2 - treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£9,976	0.311	[redacted]	[redacted]	£58,928
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation					

Public Health England

Protecting and improving the nation's health

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck – data review

Commissioned by NHS England and NHS Improvement

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Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of nivolumab for the treatment of patients diagnosed with head and neck cancer in November 2017. The appraisal committee highlighted clinical uncertainty around estimates of treatment duration and overall survival (OS) in the evidence submission. As a result, they recommended commissioning of nivolumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of nivolumab in the CDF population during the managed access period. This report presents the results of the use of nivolumab, in clinical practice, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis of data for the full patient population, with 100% of patients and 100% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for nivolumab for head and neck cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 13 October 2017 and 12 May 2019, 574 applications for nivolumab were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 506 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

All 506 (100%) unique patients with CDF applications were reported in the SACT dataset.

Median treatment duration for the analysis cohort was 3.0 months (91 days) [95% CI: 2.7, 3.3]. 28% [95% CI: 24%,32%] of patients were receiving treatment at 6 months and 17% [95% CI: 13%, 21%] of patients were receiving treatment at 12 months.

At data cut off, 78% (N=394) of patients were identified as no longer being on treatment; 63% (N=249) of patients stopped treatment due to progression, 6% (N=23) of patients stopped treatment due to acute toxicity, 3% (N=10) of patients chose to end their treatment, 8% (N=32) of patients died on treatment, 20% (N=79) of patients died not on treatment and <1% (N=1) patient stopped treatment on account of an unrelated comorbidity.

The median overall survival was 6.5 months (197 days) [95% CI:5.6, 7.6]. OS at 6 months was 52% [95% CI: 48%, 56%], OS at 12 months was 34% [95% CI: 29%, 38%].

A sensitivity analysis was conducted for a cohort with at least 6 months data follow-up in the SACT dataset. Results for treatment duration and survival were consistent with the full analysis cohort. Any differences were not significant.

Conclusion

This report analyses SACT real world data for patients treated with nivolumab for recurrent or metastatic squamous-cell carcinoma of the head and neck in the CDF. It evaluates treatment duration, overall survival and treatment outcomes for all patients treated with nivolumab for this indication.

Introduction

Head and neck cancers are rare cancer types and account for 3% of all cancer diagnoses. In 2017, 9,417 patients were diagnosed with a head and neck cancer (6,537 males, 2,880 females)[2].

Nivolumab is recommended as a treatment option for patients with squamous cell carcinoma of the head and neck whose disease has progressed on platinum based chemotherapy[3].

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From the 29th July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical and cost effectiveness. During this period of managed access, ongoing data collection is used to answer the uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE will analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee appraisal of nivolumab for recurrent or metastatic squamous-cell carcinoma of the head and neck [TA490]

The NICE Appraisal Committee reviewed the evidence for the clinical and cost effectiveness of nivolumab in treating recurrent or metastatic squamous-cell carcinoma of the head and neck [TA490] and published guidance for this indication in November 2017[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of nivolumab through the CDF for a period of 23 months, October 2017 to September 2019.

During the CDF funding period, results from ongoing clinical trials evaluating nivolumab in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. The ongoing trial to support the evaluation of nivolumab is CheckMate 141[7]. Data collected from the CheckMate 141 clinical trial would be the primary source of data collection.

Analysis of the SACT dataset would provide information on real-world treatment patterns and outcomes for nivolumab for recurrent or metastatic squamous-cell carcinoma of the head and neck in England, during the CDF funding period. This would act as a secondary source of information alongside the results of the CheckMate 141 clinical trial[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **treatment duration** for the use of nivolumab for recurrent or metastatic squamous-cell carcinoma of the head and neck
- **overall survival** from the start of a patient's first treatment with nivolumab in this indication

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (Bristol-Myers Squibb) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of nivolumab. It also detailed the eligibility criteria for patient access to nivolumab through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for nivolumab, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications - identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the EU General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of EU GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS E & I do not have an exemption to the Common Law Duty of Confidentiality, NHS E & I cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Nivolumab clinical treatment criteria

The criteria for patient access to nivolumab are:

- patient has a confirmed histological diagnosis of squamous-cell carcinoma of the head and neck
- patient has recurrent or metastatic head and neck cancer that is not amenable to local therapy with curative intent. (Local treatment is considered to be surgery and/or radiation therapy with or without chemotherapy.)
- patient's disease has progressed during or within six-months of the last dose of platinum-based chemotherapy
- patient has an ECOG performance status of 0 or 1 and would otherwise be potentially fit for docetaxel-based or methotrexate-based 2nd line chemotherapy
- patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody
- every effort has been made for the patient to have PD-L1 testing with an approved and validated test to determine the Tumour Proportion Score (TPS)

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

- if two trusts apply for nivolumab for the treatment of recurrent or metastatic squamous-cell carcinoma of the head and neck for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected

- if two trusts apply for nivolumab for the treatment of recurrent or metastatic squamous-cell carcinoma of the head and neck for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust

- if two applications are submitted for nivolumab for the treatment of recurrent or metastatic squamous-cell carcinoma of the head and neck and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected

Initial CDF cohorts

The analysis cohort is limited to the date nivolumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the pharmaceutical company. These schemes may have

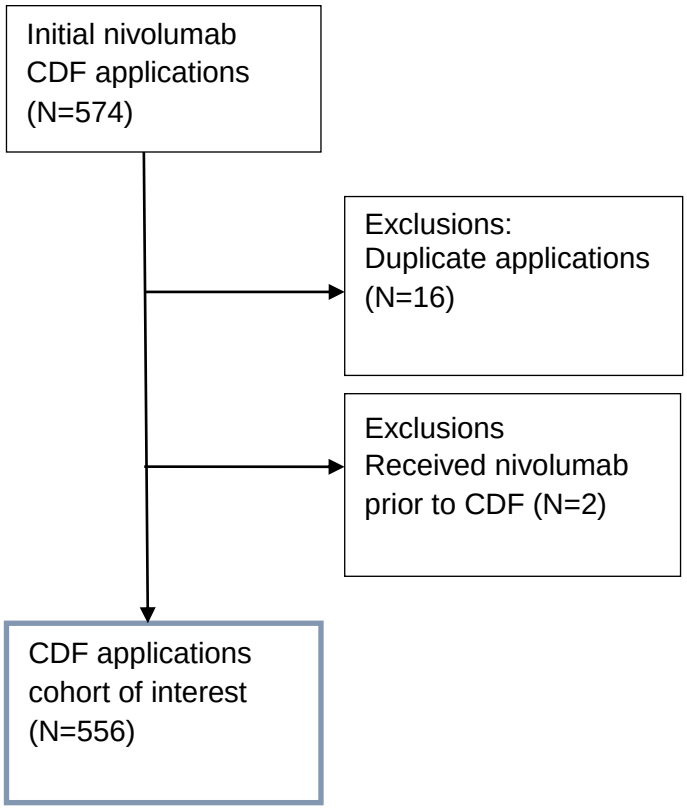
different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 13 October 2017 to 12 May 2019. A snapshot of SACT data was taken on 5 October 2019 and made available for analysis on the 14 October 2019. The snapshot includes SACT activity up to the 30 June 2019. Tracing the patients' vital status was carried out on 11 October 2019 using the personal demographics service (PDS)[1].

There were 574 applications for CDF funding for nivolumab for recurrent or metastatic squamous-cell carcinoma of the head and neck between 13 October 2017 to 12 May 2019 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 558 unique patients.

Two patients were excluded from these analyses as they appeared to have received nivolumab prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from the initial CDF applications made for nivolumab for recurrent or metastatic squamous-cell carcinoma of the head and neck between 13 October 2017 and 12 May 2019.



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for nivolumab in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were

examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a ‘prescription length’ which is a set number of days added to the final treatment date to allow for the fact that they are effectively still ‘on treatment’ between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Nivolumab is administered intra-venously. As such, treatment is generally administered in a healthcare facility and healthcare professionals are able to confirm that treatment administration has taken place on a specified date. A duration of 13-days has been added to final treatment date for all patients; this represents the duration from a patient’s last cycle to their next[9]. Nivolumab is a 14-day cycle consisting of one administration.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days).

Once a patient’s treatment duration has been calculated, the patient’s treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died
- the outcome summary (SACT data item #41) detailing the reason for stopping treatment has been completed
- there is no further SACT records for the patient following a three-month period

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead/alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) – treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

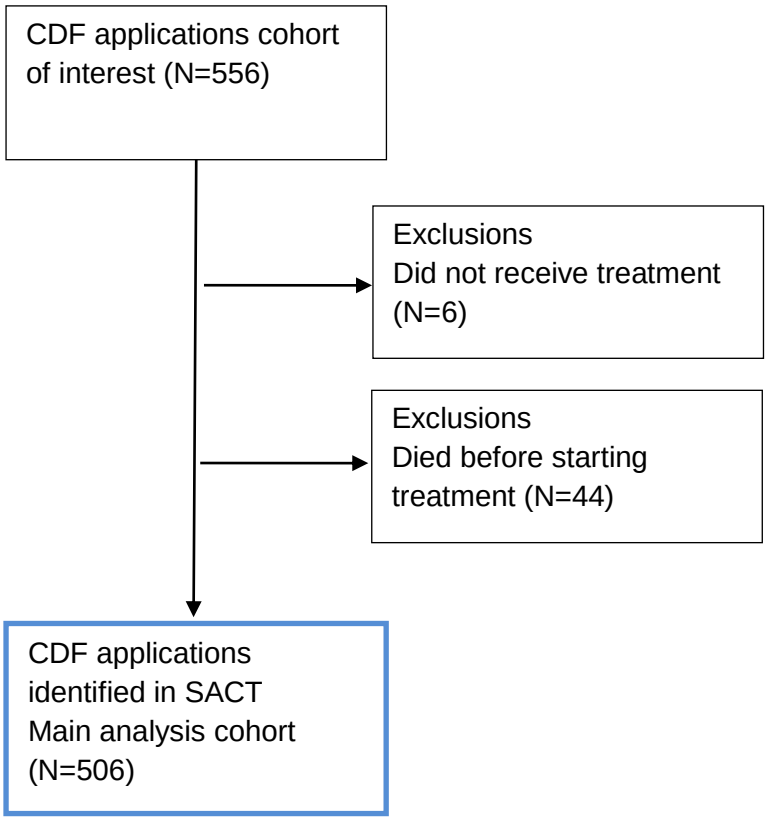
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 556 new applications for CDF funding for nivolumab for recurrent or metastatic squamous-cell carcinoma of the head and neck, six patients did not receive treatment and 44 patients died before treatment[1] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for nivolumab for recurrent or metastatic squamous-cell carcinoma of the head and neck between 13 October 2017 and 12 May 2019



A maximum of 506 nivolumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 100% (506/506) of these applicants for CDF funding have a treatment record in SACT.

[1] The six patients that did not receive treatment and 44 that died before treatment were confirmed with the relevant trusts by the PHE data liaison team.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is ≥87% for all key items and 100% for primary diagnosis, date of birth, gender and treatment dates.

Table 1: Completeness of key SACT data items for the nivolumab cohort (N=506)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	87%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with nivolumab in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 394 patients. Of these, 394 (100%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=394)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	100%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. Completeness of PD-L1 score is 58%. A test for PD-L1 status should be conducted for all patients commencing treatment with nivolumab. The patient eligibility criteria for nivolumab in patients with head and neck cancer state that "every effort should be made for the patient to have PD-L1 testing to determine the Tumour Proportion Score (TPS)" however this is not a mandatory requirement for treatment access.

Where available, clinicians were asked to submit PD-L1 test results to the NHS England and NHS Improvement Blueteq system. If there was insufficient tissue to carry out the test, clinicians were asked to report this on the Blueteq form.

The 58% completeness rate presented in Table 3 includes all applications with a PD-L1 score response. This includes patients for which the clinician stated "insufficient tissue for testing".

Table 3: Completeness of PD-L1 score in Blueteq (N=506) [2]

Variable	Completeness (%)
PD-L1 score	58%

[2] The Blueteq form for nivolumab in the indication was one of the first requesting clinicians to provide PD-L1 scores. Submission of a PDL-1 score was originally non-mandatory on the form, which resulted in high levels of missing data. The data item later became mandatory and clinicians were required to enter the PD-L1 score as a percentage Tumour Proportion Score (TPS) or select from the following option "TPS could not be quantified" or "PD-L1 testing not possible due to insufficient tissue", as documented by pathology. These requirements decreased the amount of missing data however trusts were still able to enter non-meaningful results (e.g. a single space). This issue has since been resolved but further contributed to the number of missing values.

Patient characteristics

The median age of the 506 patients receiving nivolumab for recurrent or metastatic squamous-cell carcinoma of the head and neck was 62 years. The median age in males and females was 62 and 61 years respectively.

Table 5: Patient characteristics (N=506)

Patient characteristics[2]			
		Frequency (N)	**Percentage (%)**
Sex	Male	411	81%
	Female	95	19%
Age	<40	15	3%
	40-49	39	8%
	50-59	145	29%
	60-69	194	38%
	70-79	104	21%
	80+	9	2%
Performance status	0	122	24%
	1	286	57%
	2	29	6%
	3	4	1%
	4	0	0%
	Missing/unknown	65	13%

PD-L1 distribution

The distribution of PD-L1 score in table 6 shows that 11% (N=55) of patients have a score <1%, 10% (N=52) have a score ≥1 and 37% (N=189) of patients did not have enough tissue for the test to be carried out. 42% (N=210) of patients do not have a score recorded on the Blueteq form or a reason why the test could not be carried out.

Table 6: Distribution of PD-L1 score in Blueteq (N=506)

PD-L1 score	**N**	**%**
<1	55	11%
≥1	52	10%
PD-L1 can't be quantified	189	37%
Not recorded	210	42%
Total	**506**	**100%**

[3] Figures may not sum to 100% due to rounding.

Treatment duration

Of the 506 patients with CDF applications, 394 (78%) were identified as having completed treatment by 30 June 2019 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with nivolumab in at least 3 months (see Table 7). The median follow-up time in SACT was 83.5 days.

Presently, 77% (N=108) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 21 months. 23% (N=32) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides the maximum follow-up period of 22 months. SACT follow-up ends 30 June 2019.

Table 7: Breakdown by patients' treatment status[4,5,6]

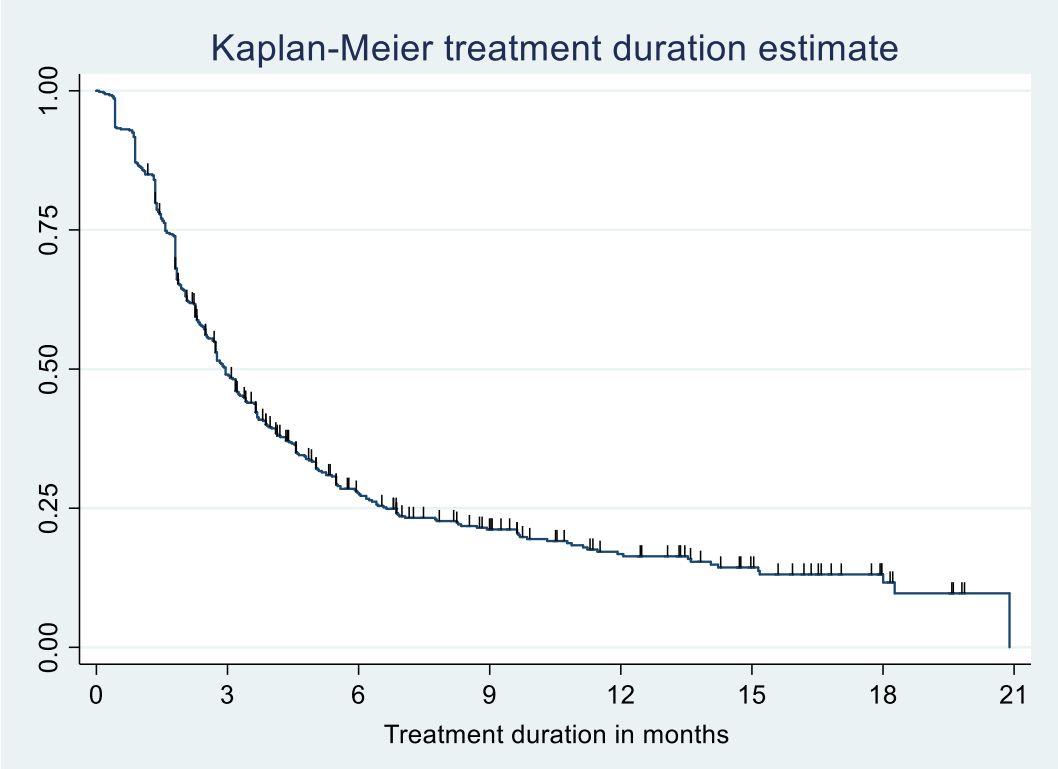
Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	303	60%
Patient died – on treatment	32	6%
Treatment stopped	59	12%
Treatment ongoing	112	22%
Total	**506**	**100%**

[4] Figures may not sum to 100% due to rounding.
[5] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 7 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[6] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 3.0 months (91 days) [95% CI: 2.7, 3.3] (N=506).

28% of patients were still receiving treatment at 6 months [95% CI: 24%,32%], 17% of patients were still receiving treatment at 12 months [95% CI: 13%, 21%].

Figure 3: Kaplan-Meier treatment duration (N=506)



Tables 8 and 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 21 months (638 days).

Table 8: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 21	3 - 21	6 - 21	9 - 21	12 - 21	15-21	18-21
Number at risk	506	234	108	65	41	23	9

Table 9 shows that for all patients who received treatment, 112 were still on treatment (censored) at the date of follow-up and 394 had ended treatment (events).

Table 9: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 21	3 - 21	6 - 21	9 - 21	12 - 21	15-21	18-21
Censored	112	94	62	43	31	18	6
Events	394	140	46	22	10	5	3

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 78% (N=394) of patients had ended treatment at 30 June 2019.

Table 10: Treatment outcomes for patients that have ended treatment (N=394)[7,8]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	249	63%
Stopped treatment – acute chemotherapy toxicity	23	6%
Stopped treatment – patient choice	10	3%
Stopped treatment – died not on treatment[9]	79	20%
Stopped treatment – died on treatment	32	8%
Stopped treatment – stopped on account of unrelated comorbidity	1	<1%
Total	**394**	**100%**

Table 11: Treatment outcomes and treatment status for patients that have ended treatment (N=394)

Outcome[10]	Patient died [11] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	201	48	
Stopped treatment – acute chemotherapy toxicity	14	9	
Stopped treatment – patient choice	9	1	
Stopped treatment – stopped on account of unrelated comorbidity		1	
Stopped treatment – died not on treatment	79		
Stopped treatment – died on treatment			32
Total	**303**	**59**	**32**

[7] Figures may not sum to 100% due to rounding.
[8] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 7 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[9] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/
[10] Relates to outcomes submitted by the trust in table 10.
[11] Relates to treatment status in table 7 for those that have ended treatment.

Overall survival

Of the 506 patients with a treatment record in SACT, the minimum follow-up was 5 months (152 days) from the last CDF application. Patients were traced for their vital status on 11 October 2019. This date was used as the follow-up date (censored date) if a patient is still alive.

The median follow-up time in SACT was 5.9 months (179 days). Figure 4 provides the Kaplan-Meier curve for overall survival, censored at 11 October 2019. The median survival for all patients was 6.5 months (197 days) [95% CI:5.6, 7.6]. Survival at 6 months was 52% [95% CI: 48%, 56%], 12 months survival was 34% [95% CI: 29%, 38%].

Figure 4: Kaplan-Meier survival plot (N=506)

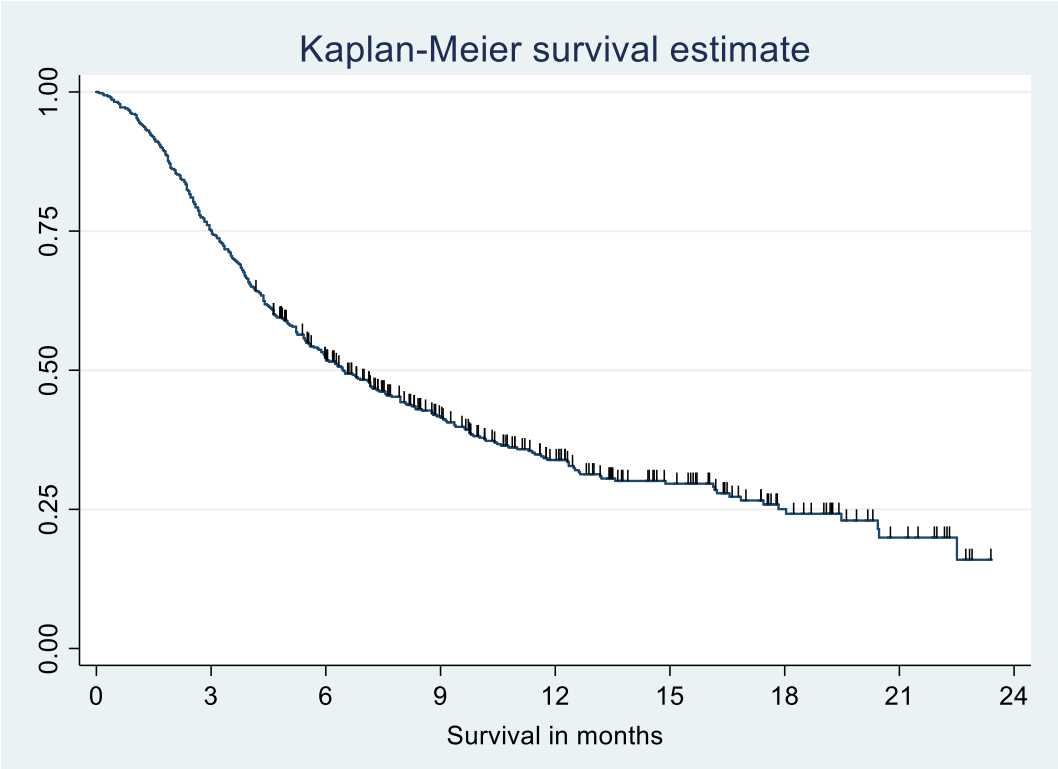


Table 12 and 13 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 24 months (730 days), all patients were traced on 11 October 2019.

Table 12: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Number at risk	506	380	246	157	98	60	30	12

Table 13 shows that for all patients who received treatment, 171 were still alive (censored) at the date of follow-up and 335 had died (events).

Table 13: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Censored	171	171	151	107	75	48	25	11
Events	335	209	95	50	23	12	5	1

Sensitivity analyses

Cohort 1: 6-month SACT follow up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least 6 months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 13 October 2017 to 31 December 2018 and SACT activity was followed up to 30 June 2019. 393 patients (78%) were included in these analyses. The median follow-up time in SACT was 87 days.

The Kaplan-Meier curve for ongoing treatment is shown in figure 5. The median treatment duration for patients in this cohort was 2.9 months (88 days) [95% CI: 2.5, 3.2] (N=393).

Figure 5: Kaplan-Meier treatment duration (N=393)

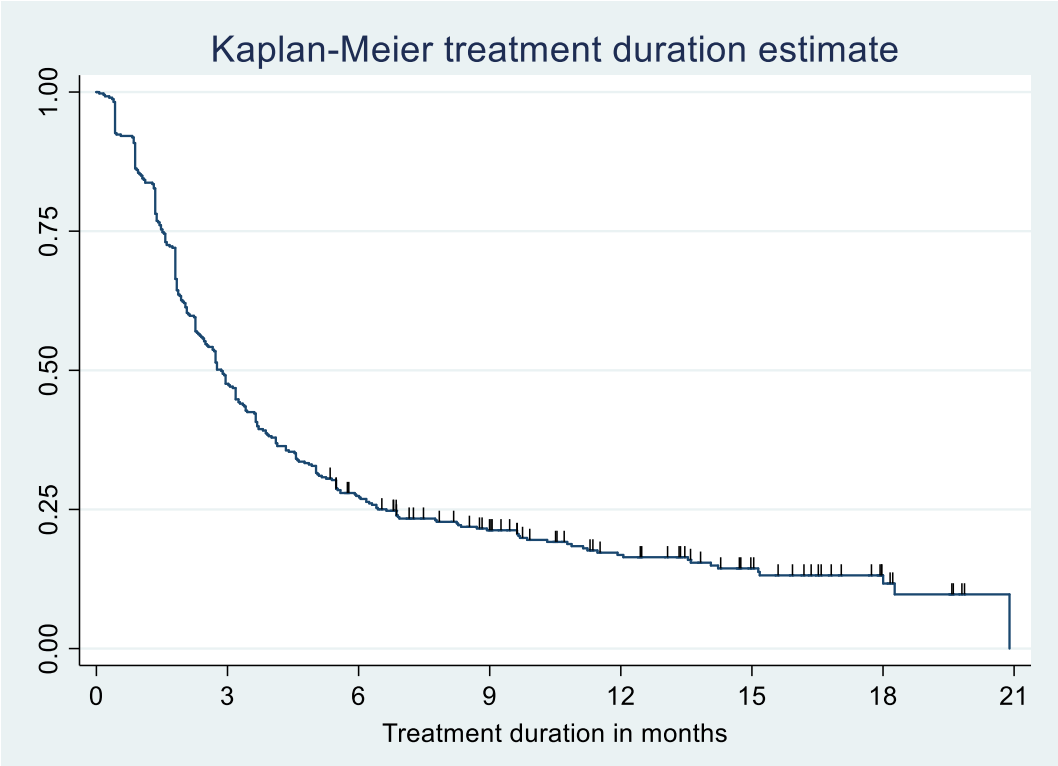


Table 14 and 15 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for treatment duration was 21 months. The minimum follow-up was 6 months.

Table 14: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	**0-21**	**3-21**	**6-21**	**9-21**	**12-21**	**15-21**	**18-21**
Number at risk	393	187	103	65	41	23	9

Table 15 shows that for all patients who received treatment, 64 were still on treatment (censored) at the date of follow-up and 329 had ended treatment (events).

Table 15: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	**0-21**	**3-21**	**6-21**	**9-21**	**12-21**	**15-21**	**18-21**
Censored	64	64	59	43	31	18	6
Events	329	123	44	22	10	5	3

Overall survival

Sensitivity analyses were also carried out for OS on a cohort with at least 6 months follow-up in SACT. To identify the cohort, CDF applications were limited from 13 October 2017 to 11 April 2019. 478 patients (94%) were included in the survival analyses with all patients having a minimum follow-up of 6 months. Follow up continued from treatment start date to date of tracing for vital status (11 October 2019). The median follow-up time in SACT was 6.2 months (188 days).

Figure 6 provides the Kaplan-Meier curve for overall survival, censored at 11 October 2019. The median survival for all patients was 6.3 months (191 days) [95% CI: 5.5, 7.4].

Figure 6: Kaplan-Meier survival plot (N=478)

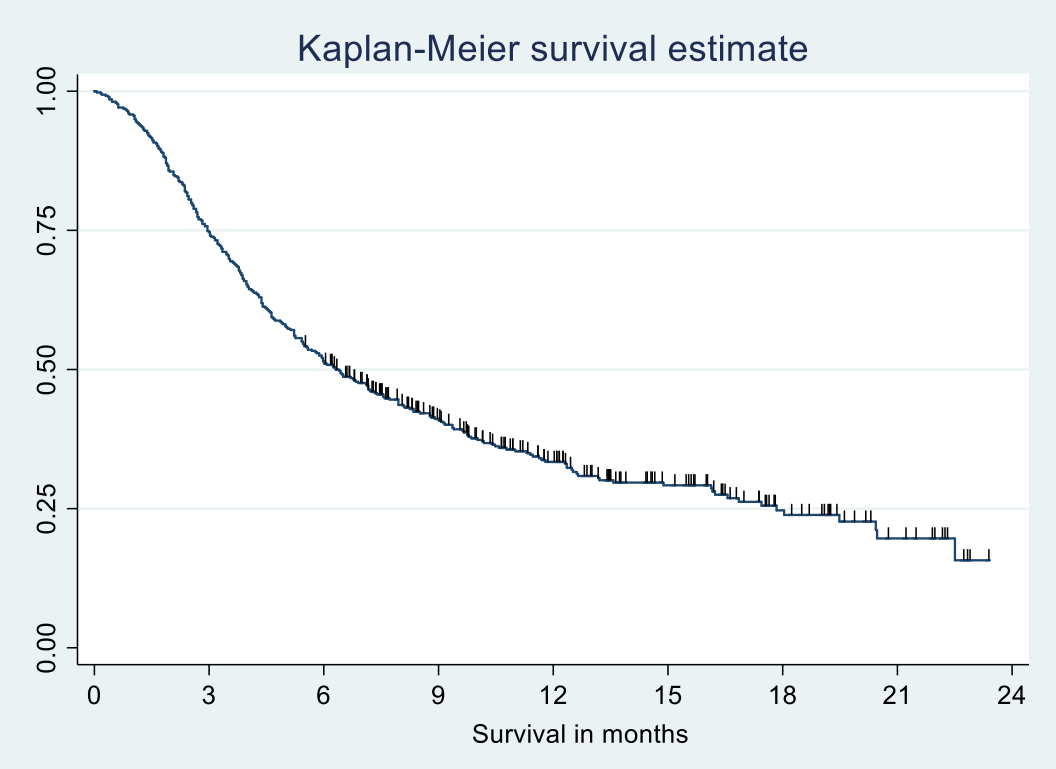


Table 16 and 17 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 24 months (730 days), all patients were traced on 11 October 2019.

Table 16: **Includes the number of patients at risk, by quarterly breakpoints.**

Time intervals (months)	**0-24**	**3-24**	**6-24**	**9-24**	**12-24**	**15-24**	**18-24**	**24**
Number at risk	478	357	245	157	98	60	30	12

Table 17 shows that for all patients who received treatment, 151 were still alive (censored) at the date of follow-up and 327 had died (events).

Table 17: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Censored	151	151	150	107	75	48	25	11
Events	327	206	95	50	23	12	5	1

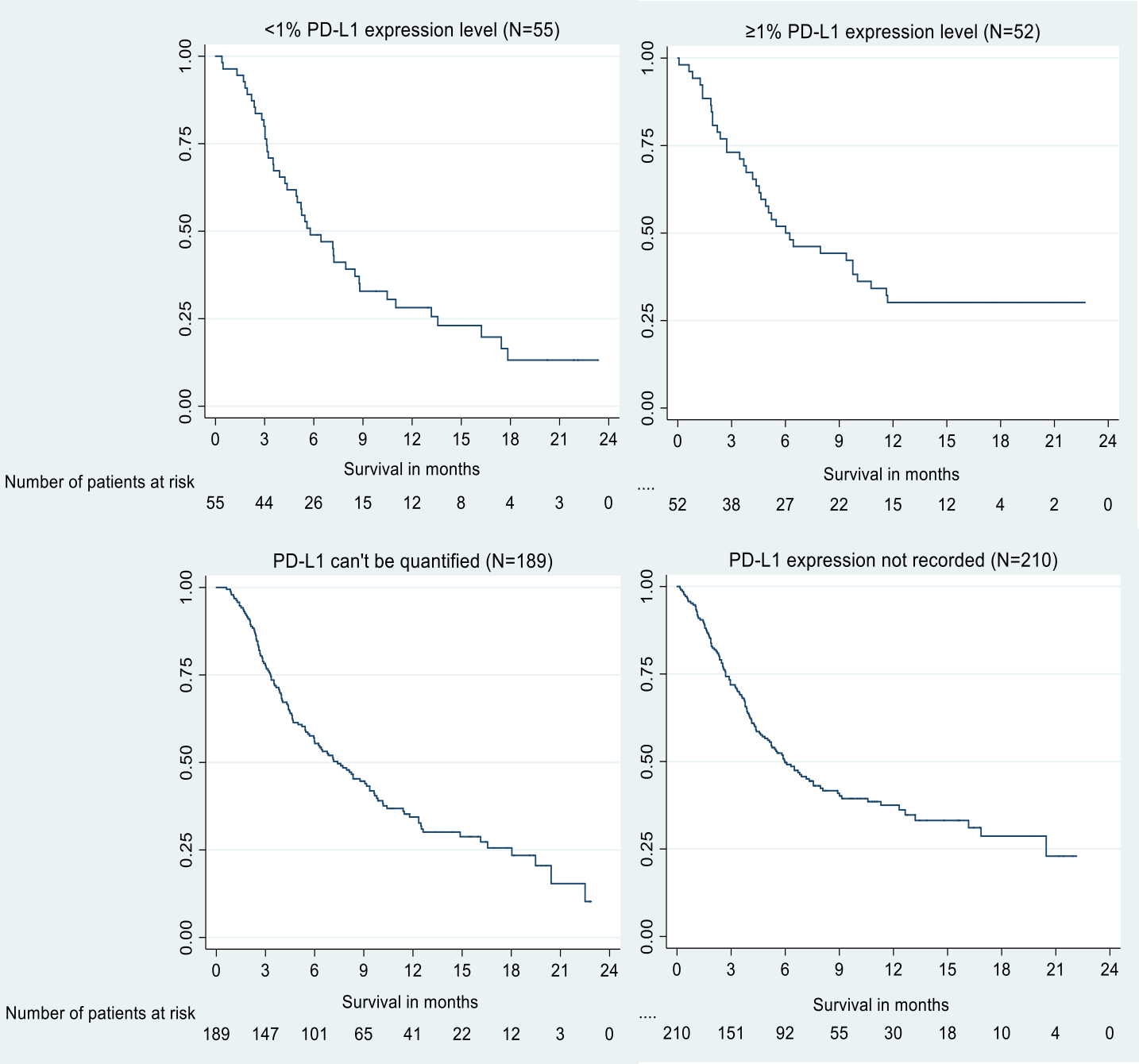
Table 18: Median treatment duration and overall survival, full cohort and sensitivity analysis.

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	506	430	478
Median treatment duration	3.0 months (91 days) [95% CI: 2.7, 3.3]	2.9 months (88 days) [95% CI: 2.5, 3.2]	
OS	6.5 months (197 days) [95% CI: 5.6, 7.6]		6.3 months (191 days) [95% CI: 5.5, 7.4]

Overall survival by PD-L1 expression level

Figure 7 provides the Kaplan-Meier curves for overall survival by PD-L1 expression level, censored at 11 October 2019.

Figure 7: Kaplan-Meier curves by PD-L1 expression level



Conclusions

506 patients received nivolumab for the treatment of recurrent or metastatic squamous-cell carcinoma of the head and neck [TA490] through the CDF in the reporting period (13 October 2017 and 12 May 2019). All 506 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 100%. An additional 50 patients with a CDF application did not receive treatment or died before treatment. This was confirmed with the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that proportionally more males received nivolumab treatment compared to females (81% (N=411) male, 19% (N=91) female). Most of the cohort was aged between 50 and 79 years (88%, N=443) and 81% (N=408) of patients had a performance status between 0 and 1 at the start of their regimen.

At the end of the data collection period, 78% (N=394) of patients were identified as no longer being on treatment. Of these, 100% (N=394) of patients had an outcome submitted by the treating trust to the SACT dataset which detailed the reason why a patient ended their treatment. 63% (N=249) of patients stopped treatment due to progression, 6% (N=23) of patients stopped treatment due to acute toxicity, 3% (N=10) of patients chose to end their treatment, 8% (N=32) of patients died on treatment, 20% (N=79) of patients died not on treatment and <1% (N=1) patient stopped treatment on account of an unrelated comorbidity.

The median treatment duration was 3.0 months (91 days) [95% CI: 2.7, 3.3]. The median follow-up was 83.5 days and the maximum follow-up was 21 months (638 days).

The median overall survival was 6.5 months (197 days) [95% CI:5.6, 7.6]. The minimum follow-up was 5 months (152 days), the maximum follow-up was 24 months (730 days).

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for this cohort were consistent with the full analysis cohort for both treatment duration (full cohort = 3.0 months; sensitivity analysis cohort = 2.9 months) and overall survival (full cohort = 6.5 months; sensitivity analysis cohort = 6.3 months). Any differences in treatment duration and survival were not statistically significant.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

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

(CDF review of TA490)

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

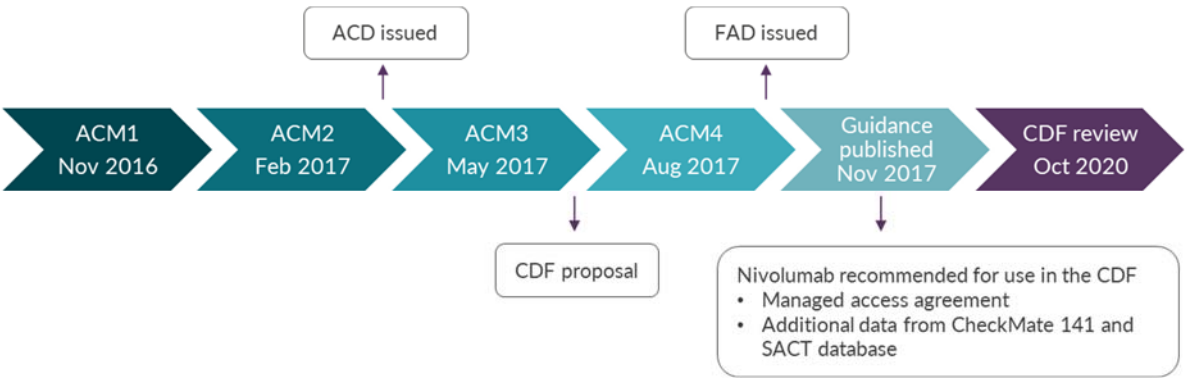
- the evidence and views submitted by the company
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: 9 October 2020

1. Topic background

1.1 Summary of original appraisal TA490



1.2 Appraisal background

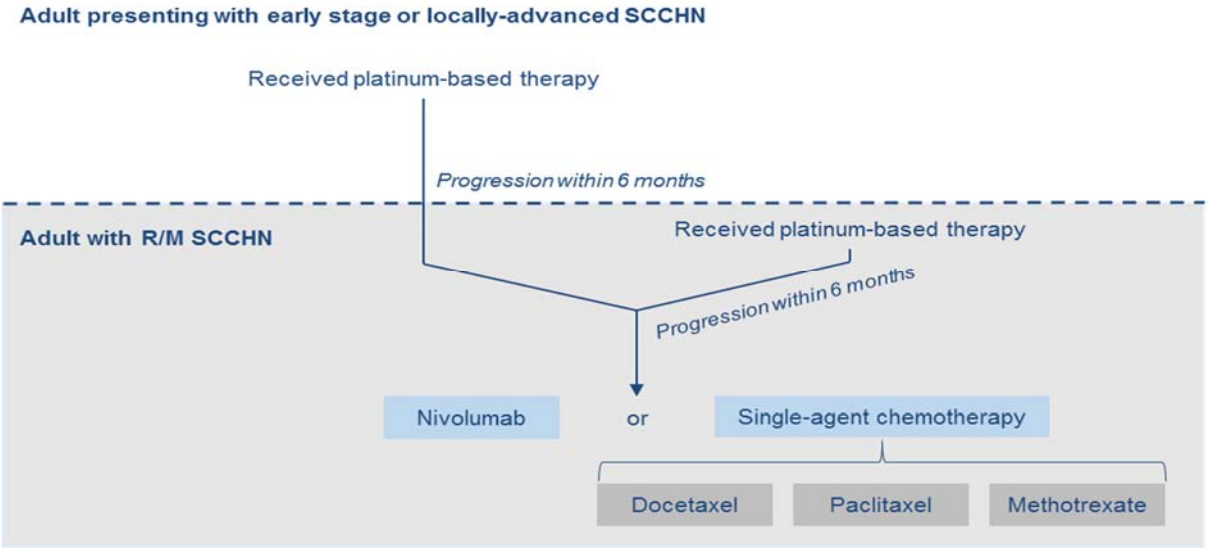
Nivolumab marketing authorisation: treatment (as monotherapy) of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.

TA490 recommendation: Nivolumab is recommended for use within the Cancer Drugs Fund (CDF) as an option for treating squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy, only if:

- The disease has progressed within 6 months of having chemotherapy
- Nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression and
- The conditions in the managed access agreement are followed.

	Original appraisal (TA490)	CDF review (ID1585)
Population	• Adults with recurrent or metastatic squamous cell carcinoma of the head and neck whose disease has progressed within 6 months of platinum-based chemotherapy (regardless of PD-L1 status) • PD-L1 ≥1% and PD-L1 subgroups also considered	• All-randomised patients (regardless of PD-L1 status) • PD-L1 ≥1% and PD-L1 <1% subgroups also presented
Comparator	• Docetaxel considered the most relevant comparator (based on investigator's choice all-randomised population) • ICER versus paclitaxel and methotrexate also presented	• Docetaxel only (based on investigator's choice all-randomised population)
Clinical data	• CheckMate 141 trial (September 2016)	• CheckMate 141 trial (4-year data; to October 2019) • Systemic anti-cancer therapy (SACT) data from 506 people (to October 2019)

1.3 Treatment pathway from TA490



1.4 Key considerations for TA490

	Committee preferred assumptions in TA490	Company base case in CDF review (ID1585)
Comparator	• Docetaxel is the preferred comparator (data from all-randomised IC treatment arm accepted)	• Docetaxel (based on all-randomised IC population)
OS extrapolation	• Nivolumab and IC: piecewise with lognormal (20, 36 and 48-week cut-off points)	• Nivolumab and IC: piecewise with lognormal (96-week cut-off point)
PFS extrapolation	• Nivolumab and IC: generalised gamma	• Nivolumab and IC: generalised gamma
TTD	• Nivolumab and IC: generalised gamma	• Nivolumab: 2-spline normal • IC: [redacted]
Utility values	• Both treatment-dependent and independent utility values considered	• Only treatment-dependent utility values included • Time-to-death utility decrements applied
2-year stopping rule	• Considered inappropriate • Accepted only as part of CDF	• Included
Duration of continued treatment effect	• 5 years	• Lifetime
Dose	• Weight-based	• Fixed dose
PAS	• [redacted]	• [redacted]

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

1.5 Key clinical data sources for CDF review

Study title	CheckMate 141 – Primary evidence source	SACT data cohort study – Supportive evidence
Study design	Multicentre, open-label, phase III randomised controlled trial	SACT data cohort study
Population	Adults with histologically confirmed recurrent or metastatic squamous cell carcinoma of the head and neck, stage III/IV, and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) and whose disease	Patients with histologically confirmed recurrent or metastatic squamous cell carcinoma of the head and neck cancer that is not amenable to local therapy with curative intent (surgery and/or radiation therapy with or without chemotherapy) and whose

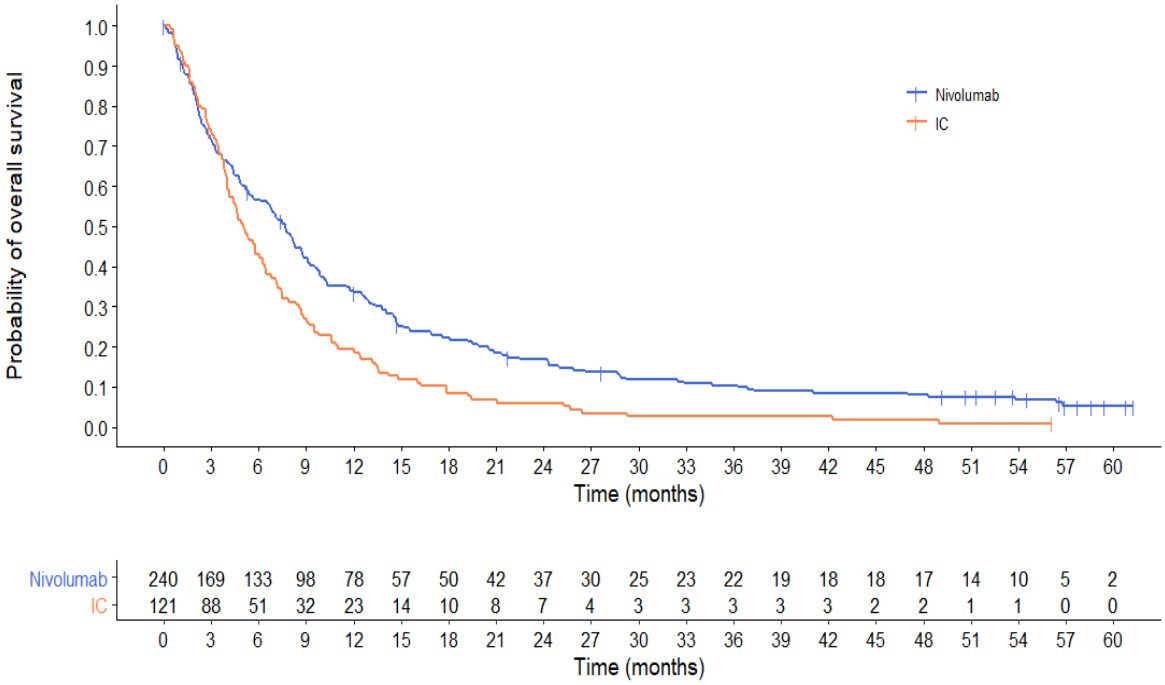
	has progressed within 6 months of last dose of platinum therapy in the adjuvant, primary, recurrent, or metastatic setting	disease has progressed during or within 6 months of the last dose of platinum-based chemotherapy
Intervention(s)	Nivolumab (weight-based dosing)	Nivolumab (weight-based or a flat dose)
Comparator(s)	Investigator's choice of chemotherapy, from: • Docetaxel • Methotrexate • Cetuximab	Not applicable
Outcomes collected	• OS, PFS, TTD • Overall and by PD-L1 status	• OS, TTD • Overall and by PD-L1 status

Source: Table 4 from company submission; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

1.6 Key trial results

Results from CheckMate 141 (data cut-off: October 2019) and SACT are shown in Figure 1, Figure 2 and Table 1 for overall survival (OS) and Figure 3, Figure 4 and Table 2 for time to treatment discontinuation (TTD). Since the original submission for TA490, data from the latest data cut-off the CheckMate 141 trial (15th October 2019; 4-year data) have become available. The minimum follow-up at this cut-off was 48.2 months (an additional 36.8 months), with 1 patient alive on the IC arm and 13 alive on the nivolumab arm [redacted]

Figure 1. Kaplan-Meier plot for OS in the all-randomised population in CheckMate 141 (data cut-off: October 2019).



Source: Figure 1 from company submission; OS: Overall survival.

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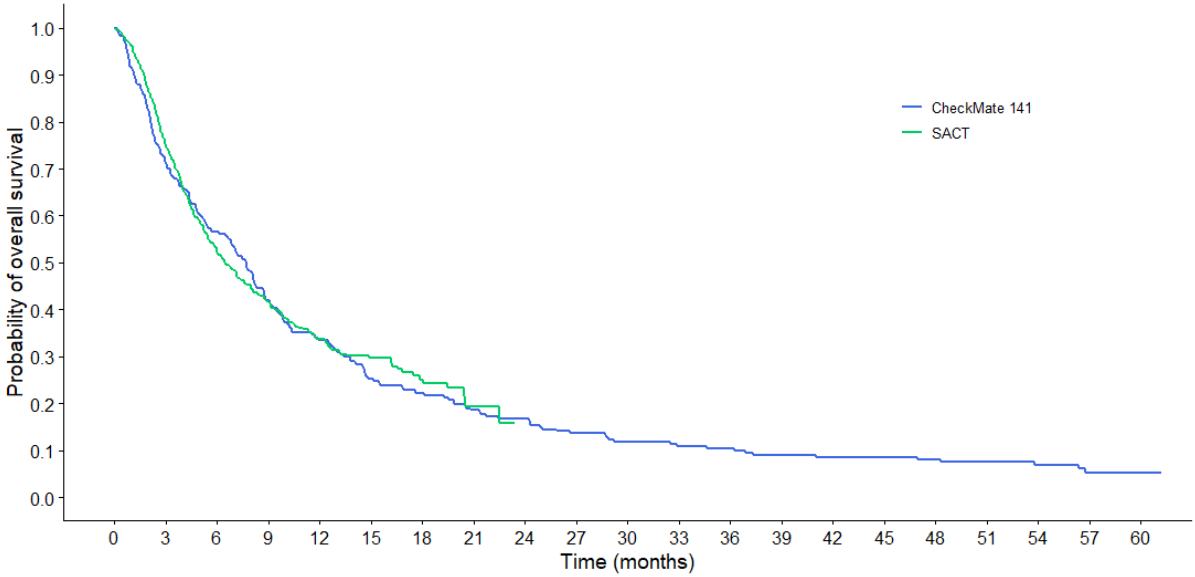
Figure 2: Kaplan-Meier plot for OS from SACT database and CheckMate 141 trial (nivolumab arm)



Source: Figure 11 from company submission; OS: overall survival.

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Table 1. Overall survival in the all-randomised population in CheckMate 141 and SACT.

Outcome	CheckMate 141 September 2016		CheckMate 141 October 2019		SACT October 2019
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=506)
Deaths, n (%)	[redacted]	[redacted]	218 (90.8)	118 (97.5)	335/506 (66.2)
Median OS, months (95% CI)	[redacted]	[redacted]	7.72 (5.68, 8.74)	5.06 (4.04, 6.24)	6.5 (5.6, 7.6)
HR for death with nivolumab (95% CI)	0.70 (97.73% CI: 0.51, 0.96)		0.69 (0.55, 0.86)		NA
12-month survival rate, % (95% CI)	[redacted]	[redacted]	33.4 (27.5, 39.5)	19.4 (12.9, 26.9)	34 (29, 38)
18-month survival rate, % (95% CI)	[redacted]	[redacted]	22.1 (17.0, 27.6)	8.4 (4.3, 14.3)	NA
24-month survival rate, % (95% CI)	[redacted]	[redacted]	16.8 (12.3, 21.9)	5.9 (2.6, 11.1)	NA
36-month survival rate, % (95% CI)	[redacted]	[redacted]	10.3 (6.8, 14.7)	2.5 (0.7, 6.6)	NA
48-month survival rate, % (95% CI)	[redacted]	[redacted]	8.0 (4.9, 12.0)	1.7 (0.3, 5.4)	NA

Source: Table 5 from company submission, table 3.4 from the ERG report; CI: confidence interval; HR: hazard ratio; IC: investigator choice; NA: not available; OS: overall survival.

Figure 3: Kaplan-Meier plot of TTD in the all-randomised population in CheckMate 141 (Data cut-off: October 2019)

Source: Figure 3 from company submission; IC: investigator's choice; TTD: time to treatment discontinuation.

Figure 4: Kaplan-Meier plot for TTD from the SACT database and CheckMate 141 trial (nivolumab arm)

Source: Figure 12 from company submission; TTD: time to treatment discontinuation.

Table 2: Summary of TTD – all-randomised population

Outcome	CheckMate 141 September 2016		CheckMate 141 October 2019		SACT October 2019
	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=240)	IC (n=121)	Nivolumab (n=506)
Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	394/506 (77.9)
Median TTD, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	3.0 (2.7, 3.3)

Source: Table 7 from company submission and Table 3.8 from the ERG report; CI: confidence interval; IC: investigator's choice; TTD: time to treatment discontinuation.

2. Summary of the technical report

2.1 In summary, the technical team considered the following:

Issue 1 Generalisability of the trial population to NHS clinical practice

Issue 2 Extrapolation of overall survival

Issue 3 Time to treatment discontinuation

Issue 4 Stopping rule and duration of treatment effect

Issue 5 Utility values

Issue 6 PD-L1 expression subgroups

2.2 The technical team recognised that the following uncertainties would remain in the CDF review analyses and could not be resolved:

- The effect of changing the licensed dosing regimen from weight-based dosing to a fixed dose is unknown.

2.3 The cost-effectiveness results for nivolumab vs. docetaxel alone include a commercial arrangement (patient access scheme) for nivolumab.

2.4 Because of the outstanding uncertainties in the evidence base (see issues 2, 3 and 4 and Table 1), the technical team was not able to determine a most plausible ICER.

2.5 Nivolumab meets the end-of-life criteria (see TA490). The updated data support this conclusion from TA490.

2.6 The company, clinical experts and patient experts consider nivolumab to be innovative in treating recurrent or metastatic SCCHN. The committee concluded that nivolumab addresses an unmet need for a debilitating condition with few treatment options. It also concluded that its preferred analysis may not capture all potential quality-of-life benefits of nivolumab.

2.7 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Generalisability of the trial population to NHS clinical practice

Questions for engagement	1. Is Checkmate 141 population generalisable to the UK population? 2. What is the most appropriate source of data for assessing nivolumab's clinical- and cost-effectiveness compared with docetaxel? a. investigator's choice (IC) in the all-randomised population b. the docetaxel subgroup (i.e. people who received docetaxel on the IC arm and who would have received docetaxel on the nivolumab arm) 3. Are clinical- and cost-effectiveness results compared with docetaxel in the all-randomised population similar to results in the docetaxel subgroup?
Background/description of issue	**Original appraisal TA490** The committee concluded that although there were some differences between the baseline characteristics of the CheckMate 141 population and the UK population, the trial was generalisable. However, it concluded that there is uncertainty about whether the comparators used in CheckMate 141 were generalisable to clinical practice in the NHS in England: • In the trial, patients randomised to the IC arm had docetaxel (47%), methotrexate (41%) or cetuximab (12%). • The trial did not include paclitaxel, which is in NICE's final scope, but it did include cetuximab, which is not in the scope and is not considered by clinical experts to be established NHS practice in England. • Methotrexate is often reserved for people who have a poorer performance status and who are less able to tolerate the toxicity of taxane-based chemotherapy. • Subgroup results from Checkmate 141 suggested that docetaxel appears to be more effective than methotrexate. • The committee concluded that docetaxel has equivalent effectiveness to paclitaxel, but not to methotrexate.

	CDF Terms of Engagement Docetaxel is the comparator of interest in the CDF review. Observational data will also be collected for nivolumab during the period of managed access via the SACT dataset to support the data collected in the clinical trial. **CDF review** **The company** noted that data collected from SACT demonstrates the generalisability of results from the CheckMate 141 trial to patients receiving nivolumab in UK clinical practice, with a similar proportion of patients reported to be alive at 12 months in both (SACT: 34% [95% CI: 29 to 38], CheckMate 141: 33.4% [95% CI: 27.5 to 39.5]). The company stated that IC all-randomised population is the most appropriate source of clinical data for this CDF review. This is because: • the study was not powered to detect differences between nivolumab and the individual therapies comprising IC; a comparison versus docetaxel alone is therefore less robust than that using the all-randomised IC population, due to the resulting small sample sizes • risk of selection bias due to broken randomisation • the committee previously decided the all-randomised population was appropriate for decision making, and the Terms of Engagement stipulates that the committee's preferred assumptions are not expected to change at the CDF review • Although docetaxel is the most relevant comparator, patients may also receive methotrexate or another taxane (i.e. paclitaxel) in standard clinical practice. The company also noted that subgroup analysis comparing nivolumab and docetaxel in patients who would receive docetaxel in the CheckMate 141 trial was performed in response to the clarification questions for the original submission. The results of this subgroup analysis were aligned with the base-case analysis (ICER versus docetaxel of £34,286 and £34,902 per QALY gained, respectively). **The ERG** explained that UK patients might be slightly older than those in the CheckMate 141 all-randomised population (Table 3), and a small number will have a worse performance status.

Patients in the SACT dataset had a numerically lower median survival than those in the nivolumab arm of Check Mate 141 (6.5 months versus 7.7 months), but 1) this was based on a much shorter median follow-up, 2) the 95% CIs overlapped and 3) 1-year survival rates were similar (34% in the SACT versus 33.4% in the trial; see Table 1 and Figure 2). People in the SACT database had a longer median time to stopping treatment than those in the CheckMate 141 trial (see Table 2 and Figure 4).

The ERG noted that given that the committee concluded that docetaxel is the most relevant comparator for nivolumab, the most appropriate evidence of effectiveness and safety versus docetaxel is that from the docetaxel subgroup, and not from the IC all-randomised patient population. The company did not provide such analyses for this CDF review.

Table 3: Baseline characteristics of patients in the CheckMate 141 trial and SACT

Characteristic	CheckMate 141; Nivolumab (n=240)	SACT data cohort study (n=506)
Male, n (%)	197 (82.1)	411 (81)
Age, median (years)	59.0	62
Age categorisation, n (%)		
<40	14 (6)	15 (3)
40-49	18 (8)	39 (8)
50-59	90 (38)	145 (29)
60-69	87 (36)	194 (38)
70-79	29 (12)	104 (21)
80+	2 (1)	9 (2)
Performance status, n (%)		
0	49 (20.4)	122 (24)
1	189 (78.8)	286 (57)
≥2	1 (0.4)	33 (7)[a]
Missing	1 (0.4)	65 (13)
PD-L1 score		
<1	73 (30.4)	55 (11)
≥1	88 (36.7)	52 (10)
Can't be quantified	79 (32.9)	189 (37)

	<table><tr><td>Not recorded</td><td>N/A</td><td>210 (42)</td></tr><tr><td colspan="3">[a] A total of 29 patients (6%) has performance status score of 2, 4 (1%) had performance status scope of 3, and none had performance status score of 4. Sources: Table 13 from Company Submission and Table 1 from the company's responses to clarification questions.</td></tr></table> **The technical team** notes that there is uncertainty in the generalisability of CheckMate 141 to NHS practice, because of small differences in patients baseline characteristics and because people in the SACT database had a longer median time to stopping treatment than those in the CheckMate 141. The technical team agrees with the company's approach to use all-randomised patient population data in the base-case analysis, but notes that sensitivity analyses based on the docetaxel subgroup using the updated trial data would be useful for decision making.
Why this issue is important	There are some differences between patients included in the SACT database and CheckMate 141 which could impact on the generalisability of the trial results to NHS clinical practice. The company did not provide scenario analyses using data from patients intended to receive docetaxel only, so the impact of this on the cost-effectiveness results is unclear.
Technical team preliminary judgement and rationale	The generalisability of the CheckMate 141 trial remains uncertain. Using the all-randomised IC population appears to be a reasonable base-case approach, but scenario analyses based on the docetaxel subgroup would be useful to validate the base-case results.

Issue 2 – Extrapolation of overall survival

Questions for engagement	4. What is the most appropriate method for extrapolating overall survival (OS) data in the 'all-randomised' population?
Background/description of issue	**Original appraisal TA490** The committee concluded that there was significantly better OS in the nivolumab group at 18-month follow up, compared with IC, but the incremental OS benefit beyond 24 months is uncertain. • The committee recognised that the most appropriate time point from which to extrapolate the trial data was uncertain and concluded that it would consider all 3 options (piecewise lognormal model where Kaplan-Meier data was extrapolated from 20, 36 and 48 weeks).

	• The committee had concerns with each of these 3 options presented and considered that the choice of an appropriate time point would be arbitrary. • It noted that varying the time points had an inconsistent effect on the model result. As the time point moved from 20 to 36 weeks, the ICER decreased, but it increased when the time point moved from 36 to 48 weeks. **CDF Terms of Engagement** OS data should be updated with the longer follow-up data from CheckMate 141. A piecewise model is expected to be used to extrapolate OS. The timepoint to extrapolate from and the distribution used should be explored in the CDF review. **CDF review** **The company** submitted a revised base-case analysis based on a piecewise method, using the Kaplan-Meier data followed by a lognormal distribution from 96 weeks to extrapolate OS • Piecewise models using the lognormal distribution provided better visual fits to the OS data than alternative curve forms (Figure 1 and Table 4**Error! Reference source not found.**). • The week 96 time point was selected to maximise the use of observed trial (Kaplan-Meier) data. • Fully parametric extrapolations of the observed data were considered in scenario analyses (Table 4**Error! Reference source not found.**). The lognormal and log-logistic curves provided best statistical fits to the data. **The ERG** agrees with the company's approach for extrapolating OS. However, it noted that this extrapolation was not externally validated by expert opinion or external data, therefore its plausibility remains uncertain. The ERG also agrees that fully parametric models may provide plausible alternatives for extrapolating OS and should be explored in sensitivity analyses. **The technical team** agrees that the company's approach may be plausible, however clinical expert opinion and/or a comparison with external data would be useful to validate this (Table 4). The technical team also agrees with the ERG that fully parametric models should be explored in sensitivity analyses.

Table 4. Comparison of OS (%) using different extrapolation methods, for both treatment arms.

Extrapolation model	1 year	2 years	3 years	4 years	5 years	10 years	15 years	20 years	25 years
Nivolumab									
CheckMate 141 (Kaplan-Meier data)	33.4	16.8	10.3	8.0	n/a	n/a	n/a	n/a	n/a
SACT (Kaplan-Meier data)	34.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Piecewise, lognormal, 96-week (company base-case)	33.4	16.1	10.1	7.3	5.7	2.6	1.5	1.0	0.8
Piecewise, lognormal, 48-week	33.8	16.2	10.1	7.1	5.3	1.9	1.0	0.6	0.4
Piecewise, lognormal, 36-week	31.8	16.3	10.8	8.0	6.2	2.6	1.5	1.0	0.7
Piecewise, lognormal, 20-week	32.9	17.1	10.9	7.6	5.7	2.0	1.0	0.6	0.4
Piecewise, exponential, 96-week[a]	33.4	16.2	11.0	7.5	5.1	0.7	0.1	0.0	0.0
Piecewise, exponential, 48-week[a]	33.7	19.1	10.8	6.1	3.5	0.2	0.0	0.0	0.0
Piecewise, exponential, 36-week[a]	36.9	19.3	10.1	5.3	2.7	0.1	0.0	0.0	0.0
Piecewise, exponential, 20-week[a]	39.7	19.0	9.1	4.4	2.1	0.1	0.0	0.0	0.0
Fully parametric, lognormal	33.6	17.3	10.6	7.2	5.2	1.6	0.7	0.4	0.2
Fully parametric, log-logistic	32.7	16.5	10.5	7.4	5.7	2.4	1.4	1.0	0.7
Investigator's choice (IC)									
CheckMate 141 (Kaplan-Meier data)	19.4	5.9	2.5	1.7	n/a	n/a	n/a	n/a	n/a

	Piecewise, lognormal, 96-week (company base-case)	19.4	5.6	2.3	1.1	0.6	0.1	0.0	0.0	0.0
	Piecewise, lognormal, 48-week	18.6	5.1	2.1	1.1	0.6	0.1	0.0	0.0	0.0
	Piecewise, lognormal, 36-week	16.3	5.7	3.1	2.0	1.4	0.4	0.2	0.1	0.1
	Piecewise, lognormal, 20-week	17.2	6.3	3.2	2.0	1.3	0.3	0.1	0.1	0.0
	Piecewise, exponential, 96-week	19.4	5.3	2.6	1.2	0.6	0.0	0.0	0.0	0.0
	Piecewise, exponential, 48-week	17.9	6.2	2.1	0.7	0.3	0.0	0.0	0.0	0.0
	Piecewise, exponential, 36-week	20.8	5.6	1.5	0.4	0.1	0.0	0.0	0.0	0.0
	Piecewise, exponential, 20-week[a]	21.5	4.9	1.1	0.3	0.1	0.0	0.0	0.0	0.0
	Fully parametric, lognormal	18.9	5.5	2.2	1.0	0.6	0.1	0.0	0.0	0.0
	Fully parametric, log-logistic	17.6	5.7	2.8	1.7	1.1	0.3	0.2	0.1	0.1
	[a] OS falls below PFS. Source: Company's model ("OS" tab); OS: overall survival; PFS: progression-free survival.									
Why this issue is important	Scenario analyses using alternative approaches for OS increase the ICER for nivolumab compared with docetaxel alone. The ICER increase ranges from an additional £1,660 to £3,924 per QALY gained when the piecewise lognormal with 48-week cut-off, fully parametric log-normal or fully parametric log-logistic approaches are used.									
Technical team preliminary judgement and rationale	The base-case piecewise model, using the Kaplan-Meier data for 96 weeks followed by a lognormal curve, appears to be reasonable for modelling OS. Expert opinion would be useful to validate the plausibility of its extrapolations as few people are still alive after 10 years. Also, parametric models are plausible alternatives and should be considered.									

Issue 3 – Time to treatment discontinuation

Questions for engagement	5. What is the most appropriate method for extrapolating time on treatment with (a) nivolumab and (b) docetaxel alone?
Background/description of issue	**Original appraisal TA490** None of the parametric distributions fitted the progression-free survival and TTD data from CheckMate 141 well. The generalised gamma distribution was the preferred distribution to model TTD. **CDF Terms of Engagement** Not applicable (no mention of TTD) **CDF review** **The company** explained that for nivolumab, the 2-spline normal model provided the best statistical fit and a reasonable visual fit to the observed TTD data from CheckMate 141 (4-year data), and was more plausible than the generalised gamma model used in TA490 (Figure 3 and Table 5) [redacted]. Additionally, the company explored using SACT data to estimate TTD (i.e. nivolumab treatment duration) in scenario analyses. **The ERG** prefers to use the generalised gamma distribution to model TTD from CheckMate 141 for both treatment arms. This is because there is no clear justification to deviate from the generalised gamma distribution used in TA490. Also, the ERG prefers not to use the [redacted]

[redacted].

The ERG also noted that the SACT data provides real-world data that might better reflect UK clinical practice than CheckMate 141. TTD in the SACT cohort was generally longer than that observed in the CheckMate 141 trial, so using the SACT data produces a higher estimate of the ICER than the base-case analysis (holding everything else constant).

The technical team notes that there is uncertainty regarding which approach is most appropriate for modelling TTD. It agrees with the company [redacted]

Using SACT data to inform TTD but not any other efficacy inputs may not be appropriate. However, the SACT data highlights high uncertainty in TTD that can be expected in real-world practice.

Table 5. Comparison of TTD (% of patients still on treatment) using different extrapolation methods, for both treatment arms.

Extrapolation model	3 months	6 months	12 months	18 months	24 months	36 months	5 years	10 years	20 years
Nivolumab									
CheckMate 141 (Kaplan-Meier data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SACT (Kaplan-Meier data)	Not reported	28	17	Not reported	n/a	n/a	n/a	n/a	n/a
2-spline normal model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator's choice (IC)									
CheckMate 141 (Kaplan-Meier data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

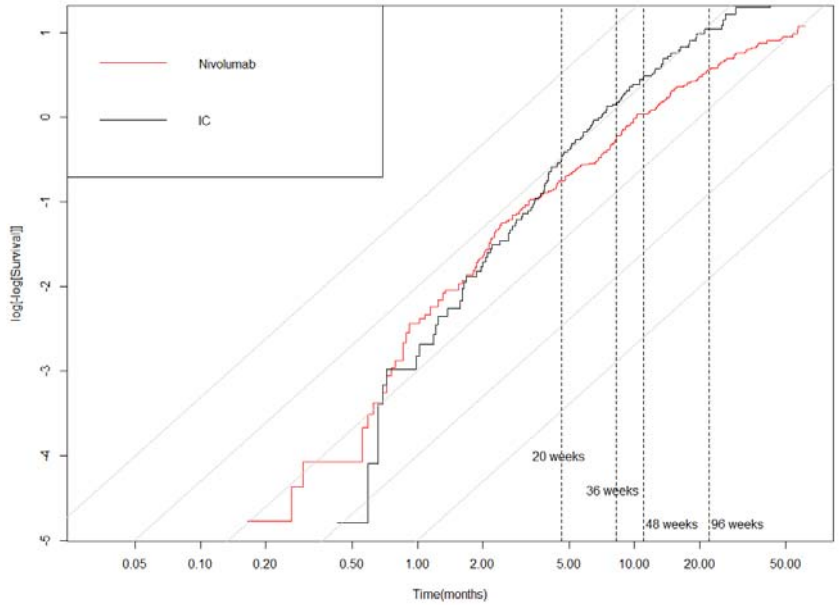
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Source: Company's model ("TTD" tab); TTD: time to treatment discontinuation.									
Why this issue is important	Using the generalised gamma distribution to model TTD for both nivolumab and IC increases the ICERs by a modest amount (+£2,604 compared with the company's base-case analysis). However, using the TTD data from SACT results in a substantially increased ICER (+£14,849 compared with the company's base-case analysis).									
Technical team preliminary judgement and rationale	The technical team agrees with the company's rationale to use the 2-spline normal model for the nivolumab arm and [redacted] for the IC arm. It is reasonable to explore the generalised gamma distribution to model TTD. Approaches that use different data sources – such as data from SACT for the IC arm to model TTD but not OS – may introduce bias due to inconsistency. However, it is important to note that the duration of treatment in real world clinical practice may be longer than observed in the pivotal trial.									

Issue 4 – Stopping rule and duration of treatment effect

Questions for engagement	6. Is a 2-year stopping rule for nivolumab appropriate? 7. If nivolumab is given for 2 years and then stopped, is it clinically plausible that its treatment benefit would continue for a lifetime? 8. If nivolumab is given for 2 years and then stopped, is it clinically plausible that its treatment benefit would continue for 3 further years (i.e. 5 years in total, the TA490 committee's preferred assumption)?
Background/description of issue	**<u>Original appraisal TA490</u>** In the original appraisal, the committee concluded that analyses without a nivolumab stopping rule are more appropriate for decision-making than analyses that included a stopping rule. The 2-year stopping rule was only accepted in the context of the CDF. • The committee noted that the stopping rule had only been applied to treatment costs and not treatment benefit.

	• It noted the comment from the company and the clinical experts that people can stop nivolumab treatment for reasons other than progression, while still having treatment benefit. • The committee was not aware of a 2-year stopping rule in the trial protocol, as seen in previous appraisals. • It noted that the company's submission stated that nivolumab treatment in the trial was allowed to continue after progression if patients were still having benefit and tolerating the drug, but the proportion of patients who were still having treatment and the average treatment duration in the trial was unclear. The committee also concluded that it is plausible that nivolumab may provide an OS benefit for up to 3 years after stopping treatment, but assuming constant benefit during this time is uncertain. **CDF Terms of Engagement** The appropriateness of a 2-year stopping rule for nivolumab and the duration of OS benefit should be reviewed in light of any new evidence. **CDF review** **The company** retained the 2-year stopping rule in its revised base case, describing it as appropriate and feasible to use in clinical practice. • The 2-year stopping rule was considered to be acceptable by clinicians and NHS England consulted as part of the original appraisal. • It was shown to be feasible during the CDF data collection. • [redacted] The company also assumed the nivolumab treatment effect continued beyond 5 years in its revised base case, referring to the updated 4-year data from the CheckMate 141 trial: • Based on the OS extrapolation used in the base case, less than 6% of patients in the nivolumab arm are predicted to be alive after 5 years (Table 4).

	• Of the 13 patients in the nivolumab arm who were alive and in follow-up, [redacted] demonstrating the durability of the survival benefit associated with nivolumab after treatment discontinuation. • Inspection of the log cumulative hazards plot shows that towards the end of the observed follow-up period of CheckMate 141 there is a difference between treatment arms in the change in hazards over time (Figure 5), with a reduction in the hazard over time in the nivolumab arm and a relatively constant hazard in the IC arm. Should this trend continue beyond the 4-year follow-up period, it would not be appropriate to assume that the hazard in the nivolumab arm becomes equal to the IC arm. **Figure 5. Log-cumulative hazard plot for OS (all-randomised population)**



Data source: Figure 13 from company submission; IC = investigator's choice; OS: overall survival.

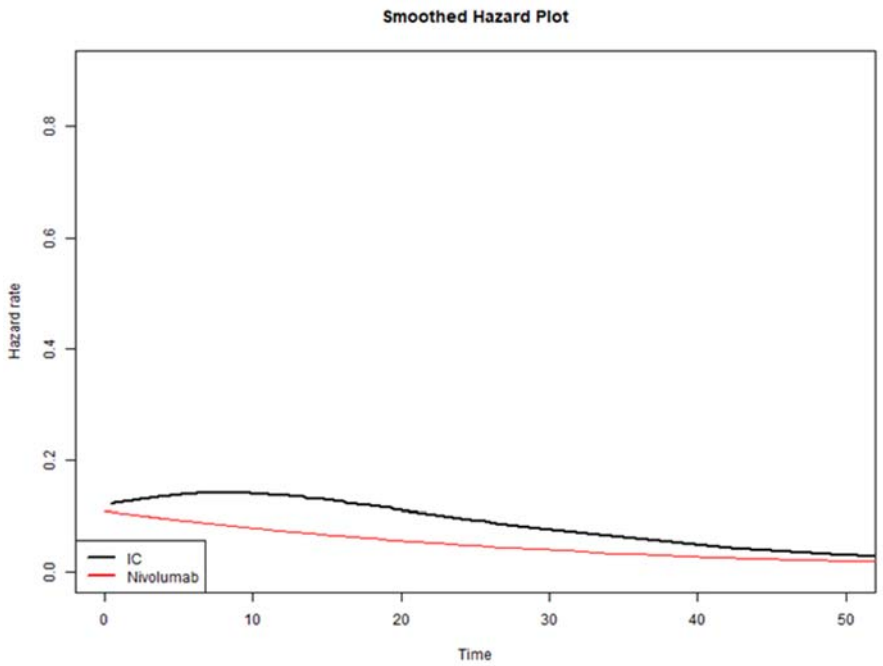
The company provided scenario analyses in which the stopping rule is removed, and where the nivolumab OS benefit lasts for 5, 7 and 10 years. The company also provided scenarios to reflect the possibility that the duration of OS benefit applies for some, but not all, patients treated with nivolumab. In these 'partial continued effect' analyses, the nivolumab treatment effect is only lost in a proportion of patients, based on whether they had a best overall response of complete response, partial response or stable disease.

The ERG prefers to exclude the 2-year stopping rule, consistent with TA490 committee preferences and with the CheckMate 141 trial design that did not include it.

The ERG noted that the assumption of a continued nivolumab OS benefit after year 5 may be inappropriate. This is because the (smoothed) hazard rates of nivolumab and IC seem to converge (Figure 6), indicating similar mortality probabilities for both treatments by 4-5 years. The CheckMate

141 trial did not have a 2-year stopping rule. If it had a 2-year stopping rule, this convergence may have occurred earlier.

Figure 6 Smoothed hazards plot for OS (all-randomised population)



Data source: Figure 2 from company responses to clarification questions; IC: investigator's choice; OS: overall survival.

The technical team notes that a 2-year stopping rule is in place for other immunotherapies in other indications (for example, pembrolizumab in TA519 and TA600). However, the trial did not include a 2-year stopping rule. If the stopping rule is maintained, there is limited evidence to inform how long the benefit from nivolumab would last after it is stopped. The technical team agrees with the ERG that assuming a continued nivolumab OS benefit after year 5 may be inappropriate. The smoothed

	hazards from CheckMate 141 appear to converge after approximately 52 months, which indicates that the nivolumab treatment effect may last for additional 3 years after stopping treatment (up to 5 years in total). It notes that very few patients were still alive in the IC arm after 2-3 years and some patients in the nivolumab arm could have durable responses. The technical team also notes that the median TTD was [redacted] and only [redacted] of 236 patients in the nivolumab treatment were still on treatment after 2 years of therapy. Overall, as there is no strong new evidence to support a longer treatment effect duration, a 5-year duration seems plausible.
Why this issue is important	Cost-effectiveness results increase when the 2-year stopping rule is removed (ICER increases by +£11,800 from the company's corrected base-case ICER of £37,254). The company's base-case ICER increases when using the TA490 committee's preferred 5-year duration of nivolumab treatment effect (by +£7,803), rather than assuming a lifetime benefit.
Technical team preliminary judgement and rationale	It is uncertain whether a 2-year stopping rule is appropriate. The technical team's preliminary judgement is not to use a stopping rule. This agrees with the committee's preference in TA490. However, as very few patients remain on nivolumab treatment after 2 years, cost-effectiveness results with and without the stopping rule should be considered. There is uncertainty about what happens to the treatment effect when treatment is stopped, because the CheckMate 141 trial did not include a stopping rule. However, 5-year treatment effect duration appears plausible.

Issue 5 – Utility values

Questions for engagement	9. Which approach to utility values is most appropriate? a. Treatment-dependent versus treatment-independent utility values b. Incorporating decrease in utility values before death (or not)
Background/description of issue	**Original appraisal TA490** The committee was concerned that the utility values calculated by the company's mixed modelling approach (based on EQ-5D-3L data from Checkmate 141) were associated with significant uncertainty. The committee noted that although the nivolumab survival benefit was stopped at 5 years in the company's scenario analysis, its quality-of-life benefit was assumed to last for the full duration of the model. It concluded that this was implausible. • The committee questioned the relatively high utility value assigned to the nivolumab arm after treatment had stopped and the disease had progressed. • The committee and the ERG also questioned the plausibility of extrapolating the high post-progression utility over the full duration of the model, and whether the utility benefit of nivolumab compared with IC would continue after treatment is stopped. The committee concluded that the most appropriate utility values were between the treatment-dependent and the treatment-independent estimates. **CDF Terms of Engagement** The utility values were associated with significant uncertainty. Further data collection of utility values was not included as part of the data collection agreement; however, the committee would welcome any new evidence on utility values if available, and: • Quality-of-life benefit cannot be assumed to remain constant, • Exploration of the most appropriate utility values should be reviewed in light of any new evidence.

CDF review

The company uses treatment-dependent utility values in its preferred base-case.

Also, it applied time-to-death disutility decrements in the last 3 model cycles (Table 6). A scenario analysis was provided removing the time-to-death disutility decrements.

Table 6. Time-to-death utility values and decrements.

Utility value	Treatment-dependent		Treatment-independent
	Nivolumab	IC	Both treatment arms
Progressed disease	[redacted]	[redacted]	[redacted]
3 months to death (3rd-to-last model cycle)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted][a]	[redacted]
2 months to death (2nd-to-last model cycle)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]
1 month to death (last model cycle)	[redacted]	[redacted]	[redacted]
Decrement	[redacted]	[redacted]	[redacted]

[a] As the time-to-death utility (57–91 days) was greater than the PD utility, no decrement was applied.
Source: Table 15 in company submission; IC: investigator's choice.

The ERG considers that both treatment-dependent and independent utilities should be considered (2 base-cases).

The ERG notes that time-to-death utility decrements do not address the TA490 committee's concerns regarding the nivolumab quality of life benefit over time. In addition, they consider that the company's approach to calculating these utilities was not completely clear (e.g. what data cut-off was used, the number of observations included, details regarding the regression model). The ERG therefore excluded the utility decrements related to time-to-death in its scenario analyses.

	The technical team notes that no relevant evidence has been provided to change the TA490 committee's preference regarding utility values.
Why this issue is important	According to univariate sensitivity analyses, utility values are one of the key drivers of uncertainty in the cost-effectiveness estimates. Using treatment-independent utility values increases the company's preferred ICER by £4,321, because this removes the long-term nivolumab quality of life benefit. Removing the time-to-death utility decrements decreases it by £1,879.
Technical team preliminary judgement and rationale	Both treatment-dependent and independent utility values should be considered in decision making, in agreement with TA490. The former is likely to be unduly optimistic, by assuming a long duration of superior quality of life even after nivolumab treatment has been stopped, while the latter may be conservative. Applying time-to-death utility decrements does not resolve this uncertainty and is less useful for decision making.

Issue 6 – PD-L1 expression subgroups

Questions for engagement	10. Does clinical- and cost-effectiveness of nivolumab vary by PD-L1 expression status?
Background/description of issue	**Original appraisal TA490** The committee concluded that there is evidence of nivolumab's benefit for tumours expressing 1% or more PD-L1 protein, but at lower expression levels the benefit is not clear. • It noted that there was early and consistent separation of the curves for the PD-L1 ≥1% subgroup but almost complete overlap of the curves for the PD-L1 <1% subgroup, during the first 5 months of therapy. Although the curves for the PD-L1 <1% subgroup separated after 5 months, the committee noted that this was based on small patient numbers; therefore, it was difficult to establish the OS benefit in this subgroup.

	CDF Terms of Engagement The potential impact of PD-L1 expression level was included as part of the data collection arrangement. **CDF review** **The company** noted that improvements in median OS with nivolumab versus IC were observed in both PD-L1 ≥1% and PD-L1 <1% subgroups of CheckMate 141. It explained that there is not sufficient evidence to suggest that the numerical improvement in OS with nivolumab versus IC is statistically significantly different between the 2 subgroups. In the PD-L1 ≥1% subgroup, people receiving nivolumab had a median OS of 8.15 (95% CI, 6.67 to 9.53) months, compared with 4.60 (95% CI, 3.81 to 5.78) months for people receiving IC. In the PD-L1 <1% subgroup, the median OS was 6.51 (95% CI, 4.37 to 11.73) months for nivolumab and 5.45 (95% CI, 3.68 to 8.54) months for IC. The hazard ratio for OS with nivolumab versus IC was 0.54 (95% CI, 0.39 to 0.76; p<0.001) in the PD-L1 ≥1% subgroup and 0.74 (95% CI, 0.50 to 1.10; p=0.138) in the PD-L1 <1% subgroup. See Table 1 for a summary of OS data in the all-randomised population. In the PD-L1 ≥1% subgroup, people receiving nivolumab had a median TTD of [redacted], compared with [redacted] with IC. In the PD-L1 <1% subgroup, the median TTD values were [redacted] for nivolumab and [redacted] for IC. See Table 2 for a summary of TTD in all-randomised population. **The ERG** explained that the nivolumab OS advantage in comparison with IC was larger for PD-L1 ≥1% subgroup and was only statistically significant for this subgroup. However, there was no significant evidence of a treatment and subgroup interaction (p=0.239), and these results should be considered with caution due to the reduced sample sizes and wider confidence intervals. The ERG explained that TTD was the only outcome which had a statistically significant interaction between treatment and PD-L1 status. **The technical team** notes that nivolumab appears to be more clinically and cost effective in people with PD-L1 ≥1% than in those with PD-L1 <1%, but there is increased uncertainty in this evidence.
Why this issue is important	Nivolumab may be more clinically and cost effective in PD-L1 ≥1% subgroup than in the PD-L1 <1%. The company's revised base-case ICER is £36,205 per QALY gained for the PD-L1 ≥1%

	subgroup. It is £46,140 per QALY gained for the PD-L1 <1% subgroup. The company's revised base-case ICER in the all-randomised population is £37,254 per QALY gained.
Technical team preliminary judgement and rationale	PD-L1 subgroups should be considered by the committee, in addition to the all-randomised population.

4. Issues for information

Tables 7 to 9 are provided to stakeholders for information only and are not included in the technical report comments table provided.

Table 7. Technical team preferred assumptions and impact on the cost-effectiveness estimates for nivolumab vs. docetaxel (deterministic analysis)

Issue	Assumptions used	ICER (change vs. base case)		
		All-randomised group	**PD-L1 ≥1% subgroup**	**PD-L1 <1% subgroup**
	Company's base-case	£37,236	£36,163	£46,309
	Corrected docetaxel dose intensity error	£37,254 (+£18)	£36,174 (+£11)	£46,339 (+£30)
	Corrected docetaxel dose intensity error and using generalized gamma curve for PFS for both nivolumab and IC arms	£37,254 (+£18)	£36,205 (+£42)	£46,140 (-£169)
1	**Use all-randomised trial data**	No change	No change	No change
2a	**OS: Kaplan-Meier data for 96 weeks followed by lognormal curve (48 weeks for PD-L1 subgroups)**	No change	£36,316 (+£153)	£46,319 (+£10)
2b	**OS: Fully parametric lognormal curve**	Impact on ICER to be determined	Impact on ICER to be determined	Impact on ICER to be determined

Issue	Assumptions used	ICER (change vs. base case)		
		All-randomised group	**PD-L1 ≥1% subgroup**	**PD-L1 <1% subgroup**
	Company's base-case	£37,236	£36,163	£46,309
	Corrected docetaxel dose intensity error	£37,254 (+£18)	£36,174 (+£11)	£46,339 (+£30)
	Corrected docetaxel dose intensity error and using generalized gamma curve for PFS for both nivolumab and IC arms	£37,254 (+£18)	£36,205 (+£42)	£46,140 (-£169)
3a	**TTD: 2-point spline normal model for nivolumab arm; [redacted] (one-spline normal curve for PD-L1 <1% subgroup)**	Impact on ICER to be determined	Impact on ICER to be determined	Impact on ICER to be determined
3b	**TTD: Generalised gamma curve for nivolumab and IC arms (one-spline normal curve for PD-L1 <1% subgroup)**	£39,840 (+£2,604)	£38,729 (+£2,566)	£45,946 (-£363)
4a	**No stopping rule**	£49,036 (+£11,800)	£46,342 (+£10,179)	£50,060 (+£3,751)
4b	**With stopping rule & 5-year OS benefit[a]**	£45,039 (+£7,803)	£43,110 (+£6,947)	£52,109 (+£5,800)
5	**Consider treatment independent (TI) and treatment dependent (TD) utilities but no time-to-death disutility decrements**	TI: £41,557(+£4,321) TD: £35,357 (-£1,879)	TI: £39,128 (+£2,965) TD: £34,745 (-£1,418)	TI: £53,929 (+£7,620) TD: £43,009 (-£3,300)
1-5 (1, 2a, 3a, 4a. 5)	**Technical team preferences combined (no stopping rule)**	Impact on ICER to be determined	Impact on ICER to be determined	Impact on ICER to be determined
1-5 (1, 2a, 3a, 4b, 5)	**Technical team preferences combined (with stopping rule & 5-year OS benefit)**	Impact on ICER to be determined	Impact on ICER to be determined	Impact on ICER to be determined

[a] A minimum function was implemented to prevent that PFS would exceed OS (implemented in cells 'Nivolumab Traces'!G11:G370 and 'Docetaxel Traces'!G11:G370).
ICER: incremental cost-effectiveness ratio; OS: overall survival; TTD: time to treatment discontinuation.

Table 8. Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Change of dosing schedule	In the original appraisal, dosing was weight based (3 mg/kg every 2 weeks) but this has since changed in the summary of product characteristics to a flat dose of 240 mg every 2 weeks. The company assume that this dose will have equivalent clinical effectiveness.	Reversing this change in dosing regimen increases the company's preferred ICER to £37,812 per QALY gained (+£576).

Table 9. Other issues for information

Issue	Comments
Innovation	The company, clinical experts and patient experts consider nivolumab to be innovative in treating recurrent or metastatic SCCHN. The committee concluded that nivolumab addresses an unmet need for a debilitating condition with few treatment options. It also concluded that its preferred analysis may not capture all potential quality-of-life benefits of nivolumab.
Equality considerations	No equalities issues have been identified by the company, consultees and their nominated clinical experts and patient experts.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy (CDF review of TA490) [ID1585]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm** on **Friday 23 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol Myers Squibb Pharmaceuticals Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of the trial population to NHS clinical practice time horizon	
1. Is Checkmate 141 population generalisable to the UK population?	• Whilst there are small differences in baseline characteristics between CheckMate 141 and the systemic anti-cancer therapy (SACT) cohort, the results observed in CheckMate 141 can be considered generalisable to the UK population. Patients in the SACT cohort were slightly older than the patients in CheckMate 141 (median age of 62.0 versus 59.0 years, respectively). Additionally, the SACT cohort included 33 (7%) patients with Eastern Cooperative Oncology Group (ECOG) performance status 2–3, and 65 (13%) patients with missing ECOG status, suggesting that nivolumab has been used in line with the European Medicines Agency (EMA) licence in this indication, which does not exclude patients based on performance status. This is broader than the original inclusion criteria for entering the CDF, which was restricted to patients with ECOG status 0–1. Despite these differences, the generalisability of outcomes from CheckMate 141 to the UK population is supported by evidence from the SACT cohort, showing strikingly similar results for survival at 12 months, which was 34% in the SACT cohort compared to 33.4% in CheckMate 141. • In the SACT cohort, at 6 and 12 months, 28% and 17% of all patients respectively were still receiving treatment, compared to [redacted]% and [redacted]% of patients in CheckMate 141. Whilst individuals in the SACT cohort had a longer median time to stopping treatment, this may be due to differences in timepoints for progression assessment between CheckMate 141 and the SACT cohort, as clinicians have suggested that patients in the UK receive a scan around 12 weeks after starting treatment to check for progression. Therefore, differences in median time to stopping treatment may not be due to differences between patient populations, and would be applicable to both treatment arms.
2. What is the most appropriate source of data for assessing nivolumab's clinical- and cost-effectiveness compared with docetaxel?	• The most appropriate source for assessing nivolumab's clinical and cost-effectiveness compared to docetaxel is the all-randomised population from CheckMate 141. Whilst docetaxel is considered to be the main comparator, feedback from a clinical expert consulted as part of this response suggests the majority of patients in UK clinical practice in this line of therapy would not receive docetaxel, and instead

a. investigator's choice (IC) in the all-randomised population
b. the docetaxel subgroup (i.e. people who received docetaxel on the IC arm and who would have received docetaxel on the nivolumab arm)

would receive no active treatment at all (i.e. palliative or best supportive care [BSC]). As a more tolerable treatment option, the introduction of nivolumab has allowed patients who would otherwise be unfit for docetaxel and have no remaining treatment options to receive an active treatment in this later line of therapy. Nivolumab is therefore used in a broader population in clinical practice than the patient population who are fit enough to receive docetaxel. Despite this, for completeness, and at the request of NICE and the ERG, the clinical effectiveness results have been provided for the patients in the CheckMate 141 'intended for docetaxel' subgroup.

- A summary of the baseline characteristics of patients included in the intended for docetaxel subgroup of CheckMate 141 versus the all-randomised population and the SACT data cohort study is presented in Table 1. There are clear similarities between the docetaxel only subgroup and the all-randomised population of the CheckMate 141 trial. [redacted] and patients had similar performance status: [redacted]% in the intended for docetaxel subgroup versus 20.4% in the all-randomised population had an ECOG score of 0, and [redacted]% versus 78.8% had an ECOG score of 1, respectively. The similarities in baseline characteristics suggest that the intended for docetaxel subgroup is no more or less generalisable to the SACT data cohort and thus UK clinical practice than the all-randomised population. Baseline characteristics for the docetaxel arm of the intended for docetaxel subgroup and the IC arm of the all-randomised population are presented in Appendix 1.

Table 1: Baseline characteristics of patients in the intended for docetaxel subgroup versus the Checkmate 141 trial and the SACT cohort study

Characteristic	CheckMate 141; Nivolumab (n=240)	CheckMate 141 (Intended for Docetaxel); Nivolumab (n=[redacted])	Characteristic	SACT data cohort study
Male, n (%)	197 (82.1)	[redacted]	Male, n (%)	411 (81)
Age, median (years)	59.0	[redacted]	Age, median (years)	62
Age categorisation, n (%)				
<40	14 (6)	[redacted]	<40	15 (3)
40-49	18 (8)	[redacted]	40-49	39 (8)

50-59	90 (38)	[redacted]	50-59	145 (29)
60-69	87 (36)	[redacted]	60-69	194 (38)
70-79	29 (12)	[redacted]	70-79	104 (21)
80+	2 (1)		80+	9 (2)
Performance status, n (%)				
0	49 (20.4)	[redacted]	0	122 (24)
1	189 (78.8)	[redacted]	1	286 (57)
≥2	1 (0.4)	[redacted]	2	29 (6)
			3	4 (1)
			4	0 (0)
Missing	1 (0.4)	[redacted]	Missing	65 (13)
PD-L1 score				
<1	76 (31.7)	[redacted]	<1	55 (11)
≥1	96 (40.0)	[redacted]	≥1	52 (10)
Can't be quantified	68 (28.3)	[redacted]	Can't be quantified	189 (37)
			Not recorded	210 (42)

Abbreviations: PD-L1: programmed death ligand 1; SACT: Systemic Anti-Cancer Therapy.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Table 4.2-1-4.2-2[1], CheckMate 141 Data on File (15th October 2019),[2] Public Health England report[3]

- As acknowledged in the technical report, it is important to note that CheckMate 141 was not powered to detect differences between nivolumab and the individual therapies comprising IC; a comparison versus docetaxel alone therefore lacks the robustness of using the all-randomised IC population, in part due to the resulting small sample sizes. The all-randomised population includes 240 patients receiving nivolumab and 121 patients receiving IC, whereas the docetaxel subgroup includes only [redacted] patients receiving nivolumab and [redacted] patients receiving docetaxel. In addition, as discussed in the response to Question 3, the clinical outcomes for the intended for docetaxel subgroup are similar to the all-randomised population, with no statistically significant difference observed in the treatment effect for OS. As such, the all-

	randomised population is the most appropriate source of data for assessing nivolumab's clinical- and cost-effectiveness compared with docetaxel. • Although docetaxel is recognised as the primary comparator, the scope of the original appraisal and the eligibility criteria for the managed access agreement, which included patients who "would otherwise be potentially fit for docetaxel-based or methotrexate-based 2nd-line chemotherapy", acknowledges that patients may also receive methotrexate or another taxane (i.e. paclitaxel) in standard clinical practice. The conclusion made by the committee in the original TA490 appraisal was that "docetaxel would be the most appropriate comparator for people fit enough to have docetaxel" (TA490 FAD; Section 3.2), and so it would be remiss to only focus on patients intended for docetaxel given the expected use of nivolumab for patients who might otherwise receive something other than docetaxel. The Terms of Engagement also stipulate that the committee's preferred assumptions are not expected to change at the CDF review. • Patients in the SACT cohort may have had worse fitness than the patient population in CheckMate 141 (the SACT cohort included 33 (7%) patients with ECOG performance status 2–3), indicating that patients in clinical practice may be more likely to be unfit to receive docetaxel than the patients in CheckMate 141. • Based on feedback from a clinical expert consulted as part of this response, the majority of patients who are not able to tolerate docetaxel due to age, fitness or comorbidities may in fact receive no active treatment in clinical practice. The introduction of nivolumab has provided a safe and effective treatment option for these patients who would otherwise have received palliative care/BSC alone. • Clinical expert feedback indicated that the Kaplan-Meier plot of overall survival (OS) for the IC arm of the CheckMate 141 trial (as shown in Figure 1) was more generalisable to patients in UK clinical practice who would be eligible for nivolumab than the Kaplan-Meier plot for the intended for docetaxel subgroup. As such, the most appropriate source for assessing nivolumab's clinical and cost-effectiveness is the all-randomised population from CheckMate 141.
3. Are clinical- and cost-effectiveness results compared with docetaxel in the all-randomised population similar to results in the docetaxel subgroup	• The results for OS, progression free survival (PFS), and time to treatment discontinuation (TTD) indicate that the clinical- and cost-effectiveness may be similar between the all-randomised population and the intended for docetaxel subgroup. However, as per the response to Question 2, the intended for docetaxel subgroup may not be fully reflective of the patients who are likely to receive nivolumab in clinical practice. Furthermore, the smaller sample size and lack of power means there is greater uncertainty and therefore the results for this subgroup should be interpreted with caution. Despite this, full analyses for the intended

	for docetaxel subgroup, including overall survival OS, PFS and TTD, as well as subgroup analyses based on PD-L1 status, are presented in Appendix 1. • The Kaplan-Meier plot of OS for the all-randomised population and the intended for docetaxel subgroup is presented in Figure 1. The Kaplan-Meier plots for both treatment arms [redacted]. A clinical expert confirmed that the divergence may be due to the relatively better fitness of the intended for docetaxel subgroup versus those in the IC arm as a whole, who are in fact more likely to be representative of patients in current clinical practice. The OS Hazard Ratios (HRs) for the all-randomised population and the intended for docetaxel subgroup are presented in Table 2. In both populations analysed, nivolumab was associated with a [redacted] compared to IC, indicated by a [redacted]. Given the smaller sample size of the intended for docetaxel subgroup, the 95% confidence intervals (CIs) associated with the HR are wider than for the all-randomised population. There is considerable overlap in the CIs of the HRs for the all-randomised population and intended for docetaxel subgroup, which means is not sufficient evidence for a statistically significant difference between these populations in terms of the treatment effect for OS. Therefore, the results could be considered similar between the two populations. In addition, results for PFS and TTD also appear to exhibit comparable trends to the all-randomised population (Appendix 1). As the clinical results can be considered similar across the two populations, it is more appropriate to use the all-randomised population for this appraisal, as it is adequately powered to detect differences between treatment arms and is most reflective of patients in this indication. • In the intended for docetaxel subgroup, [redacted] patients had PD-L1 <1% ([redacted] received nivolumab and [redacted] received docetaxel) and [redacted] had PD-L1 ≥1% ([redacted] received nivolumab and [redacted] received docetaxel). Given the extremely small numbers of patients in each treatment arm within these subgroups, as well as the risk of selection bias due to broken randomisation, the results for these subgroups are subject to high degree of uncertainty and not used for decision-making. However, the clinical results have been presented in Appendix 1 for completeness.

Figure 1: Kaplan-Meier plot of OS with nivolumab versus IC, all-randomised population and intended for docetaxel subgroup

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval, OS: overall survival, IC: investigators choice, KM: Kaplan Meier
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 2: Hazard ratio for OS with nivolumab versus IC, all-randomised population and intended for docetaxel subgroup

Population	HR for OS (95% CI; p-value)[a]
All-randomised population, versus IC	0.6858 (0.5483, 0.8579; p<0.001)
Intended for docetaxel, versus docetaxel	[redacted]

[a] Computed using unstratified Cox proportional hazards model with treatment group as the sole covariate.
Abbreviations: CI: confidence interval; HR: hazard ratio; IC: investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

- A cost-effectiveness analysis where OS, PFS and TTD data are based on the intended for docetaxel subgroup of the CheckMate-141 trial has been conducted, and the results of the analysis are presented in Table 3. All assumptions were in line with the base case analysis (as reported in Table 16 of the original evidence submission). This scenario produced a similar ICER versus docetaxel than the base case analysis (an increase of £4,442 from £37,257) but is still cost-effective. These results demonstrate that, despite the considerable uncertainty with using data from the intended for docetaxel subgroup due to the small sample size and lack of power, nivolumab is a cost-effective use of NHS resources.
- Given the high degree of uncertainty in the clinical data for the PD-L1 subgroups of the intended for docetaxel subgroup, cost-effectiveness analyses based on these data were not explored.

Table 3: Intended for docetaxel scenario analysis (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	11,213	0.85	0.46	[redacted]	0.56	[redacted]	41,695

Please note that these results include the ERG's correction to docetaxel dose intensity.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG: life years gained; PAS: Patient Access Scheme; QALYs, quality-adjusted life years.

Issue 2: Extrapolation of overall survival

4. What is the most appropriate method for extrapolating overall survival (OS) data in the 'all-randomised' population?

- As reported in the original evidence submission, the committee-preferred assumption of a piecewise approach has been used in the company base case. The lognormal distribution provided a better visual fit to the observed trial data compared to the exponential distribution when considering the committee-preferred piecewise models in TA490, and the 96-week cut-off point was selected to maximise the use of the observed trial data. These assumptions were confirmed as the most plausible by a clinical expert who was consulted as part of this response. BMS appreciate the ERG and NICE technical team's agreement with the company approach to modelling OS.
- BMS also acknowledge that fully parametric models may provide plausible alternatives for extrapolating OS, and scenarios exploring the fully parametric lognormal and loglogistic extrapolation for OS were

presented as part of the original submission. In these scenarios, the ICERs versus docetaxel were similar to the base case analysis (all within £4,000), and all were less than £50,000 per QALY gained.

- The proportion of patients alive at all timepoints was also similar across these three extrapolation methods for both treatment arms (within 1% at the majority of timepoints), as well as matching the available Kaplan-Meier data from the CheckMate-141 trial, as shown in Table 4. Ultimately, whilst the fully parametric models produced similar results, the piecewise log-normal is in line with the committee-preferred assumptions from TA490, and is therefore the preferred choice for the base case.

Table 4: Comparison of OS (%) using different extrapolation methods, for both treatment arms

Extrapolation model, years	1	2	3	4	5	10	15	20	25
Nivolumab									
CheckMate 141 (Kaplan-Meier data)	33.4	16.8	10.3	8.0	n/a	n/a	n/a	n/a	n/a
Piecewise, lognormal, 96-week (base-case)	33.4	16.1	10.1	7.3	5.7	2.6	1.5	1.0	0.8
Fully parametric, lognormal	33.6	17.3	10.6	7.2	5.2	1.6	0.7	0.4	0.2
Fully parametric, loglogistic	32.7	16.5	10.5	7.4	5.7	2.4	1.4	1.0	0.7
Investigator's choice (IC)									
CheckMate 141 (Kaplan-Meier data)	19.4	5.9	2.5	1.7	n/a	n/a	n/a	n/a	n/a
Piecewise, lognormal, 96-week (base-case)	19.4	5.6	2.3	1.1	0.6	0.1	0.0	0.0	0.0
Fully parametric, lognormal	18.9	5.5	2.2	1.0	0.6	0.1	0.0	0.0	0.0
Fully parametric, loglogistic	17.6	5.7	2.8	1.7	1.1	0.3	0.2	0.1	0.1

Abbreviations: OS: overall survival; PFS: progression-free survival
Source: Company's model ("OS" tab)

Issue 3: Time to treatment discontinuation

5. What is the most appropriate method for extrapolating time on treatment with (a) nivolumab and (b) docetaxel alone?

- For nivolumab, the 2-spline normal model provided the best statistical fit and a reasonable visual fit to the observed data, and was thus considered to be more plausible for extrapolation of TTD than the generalised gamma model used in TA490. The 2-spline model also predicted a reasonable estimate of mean TTD when compared to PFS (i.e. mean TTD and mean PFS were similar). As such, the 2-spline normal model was considered to be the most appropriate extrapolation method for nivolumab. For IC. [redacted]

	[redacted] in the CheckMate 141 trial, thus, [redacted] These assumptions were confirmed as the most plausible by a clinical expert consulted as part of this response. BMS appreciate the NICE technical team's agreement with the company approach to modelling time to discontinuation (TTD). • The use of TTD data from the SACT cohort for the cost-effectiveness model was explored as part of the response to the ERG clarification questions. The observed TTD for nivolumab in the SACT cohort was generally higher than the CheckMate 141 trial, as shown in the company evidence submission. The use of TTD data from the SACT cohort in the cost-effectiveness analysis therefore produced a higher estimate of the ICER than the base case analysis (i.e. using data from CheckMate 141) due to the increased costs related to treatment that were accrued in the nivolumab arm. In this analysis, uncertainty in the long-term extrapolation of TTD was largely mitigated by the inclusion of the 2-year stopping rule, and so the relative immaturity of the SACT TTD data was less of a concern. However, in a scenario where a stopping rule is not applied, the relative immaturity of the SACT TTD data would introduce considerable uncertainty in the long-term extrapolation of TTD. • Additionally, the SACT cohort does not include patients receiving IC, so cannot inform TTD for the comparator arm. As per the response to Question 1, the higher TTD observed for individuals in the SACT cohort may have been due to differences between the CheckMate 141 trial and the SACT cohort with respect to the timepoints for progression assessment, as clinicians have suggested that patients in the UK receive a scan around 12 weeks after starting treatment to check for progression (regardless of the treatment given). As such, a higher TTD may be expected in clinical practice than observed in CheckMate 141 for patients currently receiving IC. Therefore, as per the technical report, BMS agree that it would be inappropriate to use the SACT cohort TTD data to inform model parameters for nivolumab, since this would be inconsistent with the source of TTD data for IC, as well as OS and PFS data.
Issue 4: Stopping rule and duration of treatment effect	
6. Is a 2-year stopping rule for nivolumab appropriate?	• A stopping rule was included in the base case analysis of the company evidence submission. The use of a stopping rule in routine clinical practice was considered to be acceptable by clinicians consulted as part of TA490 (FAD Committee Papers 2 and 3; Comments on the ACD) and also NHS England (ACD

	Committee Papers 5; NHS England statement). Furthermore, based on the TTD extrapolation used in the base case, [redacted] of patients were predicted to still be receiving nivolumab after two years of treatment. Additionally, the incorporation of a two-year stopping rule was shown to be feasible during the CDF data collection phase. • Stopping rules have been accepted for nivolumab in other indications. In TA484, the committee considered that it was biologically plausible that the effects of nivolumab might continue after treatment stops, although the exact continued effect was uncertain. The committee noted comments on the appraisal consultation documents made by NHS England and other consultees that a 2-year stopping rule was acceptable to both patients and clinicians and would be implementable. The committee therefore accepted the stopping rule, despite the fact that no stopping rule was applied in the pivotal clinical trial (CheckMate 037).[4] More recently, a stopping rule was accepted in TA655, which is indicated for a similar tumour type (metastatic squamous non-small-cell lung cancer [NSCLC]).[5] • A stopping rule has also recently been accepted in a NICE appraisal of pembrolizumab in a similar SCCHN indication (untreated metastatic or unresectable recurrent SCCHN; ID1140).[6] • Based on the arguments above, BMS believes a stopping rule is appropriate for nivolumab.
7. If nivolumab is given for 2 years and then stopped, is it clinically plausible that its treatment benefit would continue for a lifetime?	• Nivolumab has an innovative mechanism of action, blocking PD-1 on T cells, thus promoting long term anti-tumour immunity by stimulating the immune system, rather than targeting cancer cells directly. Accumulating evidence suggests that treatment with PD-L1 inhibitors such as nivolumab may facilitate longer term benefit following treatment discontinuation. • A two-year stopping rule was implemented in KeyNote-010, a Phase III randomised trial for pembrolizumab versus docetaxel in participants with previously treated, PD-L1-positive, advanced non-small cell lung cancer (NSCLC). Of the 47 patients that completed two years of treatment, only two patients (4%) experienced progression.[7] • A pooled analysis of Phase II and III studies by Schadendorf *et al.* (2017) sought to measure the efficacy and safety of nivolumab plus ipilimumab in patients with advanced melanoma who discontinued treatment because of adverse events (AEs). Efficacy outcomes appeared similar between patients who discontinued treatment due to experiencing AEs during the induction phase and those who did not discontinue due to AEs. At a minimum follow-up of 18 months, median PFS was 8.4 months for patients who discontinued

	versus 10.8 months for those who did discontinue. Furthermore, the ORR in discontinuers was 58.3% versus 50.2% in those that did not discontinue.[8] These results demonstrate that even after discontinuation, many patients may continue to derive benefit from PD-L1 inhibitors. • A dose escalation study (CA209003) evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumours incorporated a two-year stopping rule. Sixteen patients with NSCLC discontinued nivolumab after two years of treatment. Of these patients, 12 remained alive and progression free without the need for subsequent therapy.[9] • In line with PD-L1 inhibitors in other indications, of the 13 patients in the nivolumab arm of the CheckMate 141 trial who were alive and in follow-up, [redacted], demonstrating the durability of the survival benefit associated with nivolumab after treatment discontinuation.[2] • Therefore, based on the arguments above, it is appropriate to assume that treatment benefit will continue in patients who discontinue nivolumab after two years.
8. If nivolumab is given for 2 years and then stopped, is it clinically plausible that its treatment benefit would continue for 3 further years (i.e. 5 years in total, the TA490 committee's preferred assumption)?	• As per the response to Question 7, there is accumulating evidence to suggest that treatment with PD-L1 inhibitors, including nivolumab, may facilitate longer term benefit even following treatment discontinuation. • As reported in the original submission, inspection of the log cumulative hazards plot showed that towards the end of the observed follow-up period for CheckMate 141 there was a difference between treatment arms in the change in hazards over time, with a reduction in the hazard over time in the nivolumab arm and a relatively constant hazard in the IC arm. Should this trend continue beyond the 4-year follow-up period, it would not be appropriate to assume that the hazard in the nivolumab arm becomes equal to the IC arm. However, BMS acknowledge that smoothed hazards from CheckMate 141 appear to converge after approximately 52 months, which may indicate that the nivolumab treatment effect may last for additional 3 years after stopping treatment (up to 5 years in total). • To reflect the possibility that some patients treated with nivolumab may maintain improvements in survival beyond the timepoints used in the treatment waning scenarios (5, 7 and 10 years), analyses were also conducted in which the treatment waning effect (i.e. setting the probability of death to be the same as IC) was only applied to a proportion of patients, with the remaining patients having survival modelled based on the chosen extrapolation. In these "partial" treatment waning scenarios, the proportion of patients for

	whom the treatment waning effect was not applied was based on the proportion of patients in CheckMate 141 who achieved a best overall response of complete response, partial response or stable disease ([redacted]%). As per the response to Question 7, some patients receiving nivolumab experience a durable response, which is expected to result in longer term benefit even following treatment discontinuation. Across all three scenarios, ICERs were similar to the base case (as shown in Table 22 of the original submission).
Issue 5: Utility values	
9. Which approach to utility values is most appropriate? a. Treatment-dependent versus treatment-independent utility values b. incorporating decrease in utility values before death (or not)	• The treatment-specific utility values for PF and PD have been used in the revised base case analysis to reflect the benefits in health-related quality of life (HRQoL) that are provided with nivolumab, as was recognised by clinical experts consulted as part of TA490. These utility values were derived from EQ-5D data collected during the CheckMate 141 trial and demonstrate the improved utility post-progression for patients who were randomised to receive nivolumab versus IC. The mixed model that included progression status and treatment arm (used to derive treatment-specific utility values) was associated with a better statistical fit than the model including progression status alone (treatment-independent utility values). Therefore, the treatment-dependent model should be used as the base case for decision-making. • Clinical expert feedback sought as part of this response suggested that patients who remain on nivolumab for more than a few months and respond well to treatment are more likely to experience a utility benefit post-progression. Therefore, whilst it is recognised that some patients receiving nivolumab may discontinue treatment or progress quickly (and therefore may be expected to have similar utility post-progression to patients who receive IC), the true utility values for the cohort as a whole are likely to lie closer to treatment-dependent than to treatment-independent values. • Given the differences between the nivolumab and IC arms in the number of EQ-5D observations, particularly post-progression (n=[redacted] for nivolumab and n=[redacted] for IC), the treatment-independent utility values are mainly driven by the experiences of patients in the nivolumab treatment arm. As well as failing to account for potential differences between treatment arms, these values are therefore also not considered to be an accurate reflection of the utility of patients who receive IC. • In order to address the concerns raised in TA490 about utility remaining constant over time, the economic model submitted as part of the original evidence submission includes the option to apply decrements in

	utility based on time to death. Specifically, utility decrements can be applied for the proportion of patients who are predicted to die within the next three model cycles, with separate decrements applied based on whether patients are one (0–28 days), two (29–56 days) or three (57–84 days) cycles from death. When these decrements are applied, patients in the nivolumab arm who are in the progressed disease state are initially assumed to have improved utility compared to patients in the IC arm, but as they patients approach death they experience worsening utility. It is also assumed that utility prior to death is the same regardless of treatment arm (i.e. decrements applied to the nivolumab arm were larger than those applied to the IC arm, as shown in Table 15 of the original evidence submission, such that patients experienced treatment-independent utility prior to death). The resulting ICER lies between the ICERs produced when treatment-dependent and treatment-independent utility values are applied individually. • A number of prior NICE appraisals for cancer immunotherapies have accepted the use of time-to-death utility values. Examples include ipilimumab for previously untreated advanced melanoma (TA319) and pembrolizumab for untreated metastatic squamous non-small-cell lung cancer (TA600).[10, 11] Notably, a previous submission for nivolumab for advanced melanoma (TA384) also included time-to-death utility values.[12] • Based on the arguments above, BMS believe that the most plausible approach is to use the treatment-dependent utility values with decrements applied based on time to death.
Issue 6: PD-L1 expression subgroups	
10. Does clinical- and cost-effectiveness of nivolumab vary by PD-L1 expression status?	• The clinical effectiveness results by PD-L1 status should be interpreted with caution, as CheckMate 141 was not powered to detect a difference between treatment arms in these subgroups. The overlap between the 95% CI of HRs for nivolumab versus IC in each of the PD-L1 subgroups demonstrates that there is no statistically significant difference between the subgroups in the treatment effect on OS. The HRs themselves do indicate that treatment with nivolumab is of benefit versus standard of care, regardless of PD-L1 status. • BMS believe that the evidence is such that the all-randomised population should be considered as the patient population within the CDF review. The implications of providing a recommendation based on PD-L1 status would mean patients who would benefit from treatment are denied access (either due to inconclusive tests [as demonstrated in the SACT cohort, where 79% of patients had missing or

	inconclusive PD-L1 data], or due to the occurrence of false negatives). This may introduce equity issues based on availability of testing.

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Appendix 1 – Clinical evidence for the docetaxel subgroup

The results for the intended for docetaxel subgroup (i.e. people who received docetaxel on the IC arm and who would have received docetaxel on the nivolumab arm) from the latest data cut of the CheckMate 141 trial (15th October 2019) (OS, PFS and TTD) are provided below. CheckMate 141 was not powered to detect differences between nivolumab and the individual therapies comprising IC. As such, the results of the following analyses should be interpreted with caution.

The baseline characteristics of the all-randomised population and the intended for docetaxel subgroup are presented in Table 5. In the nivolumab arms, [redacted] and patients had similar performance status: [redacted]% patients in the intended for docetaxel subgroup versus 20.4% in the all-randomised population had an ECOG score of 0, and [redacted]% versus 78.8% had an ECOG score of 1, respectively. Similarly, median age was [redacted]. Patients also had similar performance status: [redacted]% patients in the docetaxel arm versus 19.0% in the IC arm had an ECOG score of 0, and [redacted]% versus 77.7% had an ECOG score of 1, respectively.

Table 5: Baseline characteristics of patients in the intended for docetaxel subgroup versus the Checkmate 141 trial and the SACT cohort

Characteristic	CheckMate 141; Nivolumab (n=240)	CheckMate 141; IC (n=121)	CheckMate 141 (Intended for Docetaxel); Nivolumab (n=[redacted])	CheckMate 141 (Intended for Docetaxel); Docetaxel (n=[redacted])	Characteristic	SACT data cohort study
Male, n (%)	197 (82.1)	103 (85.1)	[redacted]	[redacted]	Male, n (%)	411 (81)
Age, median (years)	59.0	61.0	[redacted]	[redacted]	Age, median (years)	62
Age categorisation, n (%)						
<40	14 (6)	8 (7)	[redacted]	[redacted]	<40	15 (3)
40-49	18 (8)	14 (12)	[redacted]	[redacted]	40-49	39 (8)
50-59	90 (38)	35 (29)	[redacted]	[redacted]	50-59	145 (29)
60-69	87 (36)	41 (34)	[redacted]	[redacted]	60-69	194 (38)
70-79	29 (12)	23 (19)	[redacted]	[redacted]	70-79	104 (21)
80+	2 (1)	0 (0)			80+	9 (2)
Performance status, n (%)						
0	49 (20.4)	23 (19.0)	[redacted]	[redacted]	0	122 (24)
1	189 (78.8)	94 (77.7)	[redacted]	[redacted]	1	286 (57)
≥2	1 (0.4)	3 (2.5)	[redacted]	[redacted]	2	29 (6)
					3	4 (1)
					4	0 (0)
Missing	1 (0.4)	1 (0.8)	[redacted]	[redacted]	Missing	65 (13)
PD-L1 score						
<1	76 (31.7)	61 (50.4)	[redacted]	[redacted]	<1	55 (11)
≥1	96 (40.0)	40 (33.1)	[redacted]	[redacted]	≥1	52 (10)
Can't be quantified	68 (28.3)	20 (16.5)	[redacted]	[redacted]	Can't be quantified	189 (37)
					Not recorded	210 (42)

Abbreviations: PD-L1: programmed death ligand 1; SACT: Systemic Anti-Cancer Therapy.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Table 4.2-1-4.2-2[1], CheckMate 141 Data on File (15th October 2019),[2] Public Health England report[3]

Overall survival

The Kaplan-Meier plot of OS for the intended for docetaxel subgroup of the CheckMate 141 trial (15th October 2019) is presented in Figure 2. As shown in Table 6, the [redacted] at the time of the latest data cut of the CheckMate 141 trial. The [redacted] associated with nivolumab can also be seen in the Kaplan-Meier curves, which show a [redacted]. These additional data from the latest data cut of the CheckMate 141 trial clearly demonstrate that, as for the all-randomised population, [redacted] compared to the docetaxel subgroup.

Figure 2: Kaplan-Meier plot of overall survival in the intended for docetaxel subgroup of CheckMate 141

Data cut-off: 15th October 2019
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 6: Summary of overall survival – intended for docetaxel subgroup

Outcome	Data cut-off: 15th October 2019	
	Nivolumab (n=[redacted])	Docetaxel (n=[redacted])
Deaths, n/N (%)	[redacted])	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
12-month survival rate, % (95% CI)	[redacted]	[redacted]
18-month survival rate, % (95% CI)	[redacted]	[redacted]
24-month survival rate, % (95% CI)	[redacted]	[redacted]
36-month survival rate, % (95% CI)	[redacted]	[redacted]
48-month survival rate, % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IC: investigator's choice; NA: not applicable; OS: overall survival.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Progression-free survival

The Kaplan-Meier plot of PFS for the intended for docetaxel subgroup from the latest data cut is presented in Figure 3. A summary of PFS for the intended for docetaxel subgroup of the CheckMate 141 trial (15th October 2019) is presented in Table 7. As per the all-randomised population, [redacted]. However, as shown in Figure 3, there [redacted] and [redacted]. As shown in Table 7 and the Kaplan-Meier curves, the [redacted], in terms of [redacted], also [redacted], with a [redacted].

Figure 3: Kaplan-Meier plot of progression-free survival in the intended for docetaxel subgroup in CheckMate 141

Data cut-off: 15th October 2019
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 7: Summary of progression-free survival – intended for docetaxel subgroup

Outcome	Data cut-off: 15th October 2019	
	Nivolumab (n=[redacted])	IC (n=[redacted])
Events, n/N (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
6-month PFS rate, % (95% CI)	[redacted]	[redacted]
12-month PFS rate, % (95% CI)	[redacted]	[redacted]
18-month PFS rate, % (95% CI)	[redacted]	[redacted]
24-month PFS rate, % (95% CI)	[redacted]	[redacted]
36-month PFS rate, % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; IC: investigator's choice; NA: not applicable; PFS: progression free survival.

Source: CheckMate 141 Data on File (15th October 2019)[2]

Time to treatment discontinuation

A summary of TTD for the intended for docetaxel subgroup of the CheckMate 141 trial (15th October 2019) is presented in Table 8. The Kaplan-Meier plot of TTD for the intended for docetaxel subgroup from the latest data cut is presented in in Figure 4. As for the all-randomised population, whilst median TTD is similar between the nivolumab and docetaxel arms ([redacted] months [95% CI, [redacted], [redacted]] for nivolumab versus [redacted] months [95% CI, [redacted], [redacted]] for IC), there is separation of the Kaplan-Meier curves from approximately [redacted] months.

Figure 4: Kaplan-Meier plot of time to treatment discontinuation in the all-randomised population in CheckMate 141

Data cut-off: 15th October 2019
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 8: Summary of time to treatment discontinuation – intended for docetaxel subgroup

Outcome	Data cut-off: 15th October 2019	
	Nivolumab (n=88)	IC (n=52)
Events, n/N (%)	[redacted]	[redacted]
Median TTD, months (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; IC: investigator's choice; TTD: time to treatment discontinuation.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Figure 5.1-1,[1] CheckMate 141 Data on File (15th October 2019)[2]

Results from the PD-L1 subgroups (<1% and ≥1%)

CheckMate 141 was not powered to detect differences between treatment arms in the different PD-L1 patient subgroups of the all-randomised population, nor to detect differences between nivolumab and the individual therapies comprising IC. Due to the resulting small sample sizes, the results of these subgroup analyses should be interpreted with considerable caution.

The hazard ratios (HRs) for OS for the intended for docetaxel subgroup from the latest data cut (15th October 2019) are presented in Table 9. In each of the populations analysed (full population or PD-L1 subgroups), nivolumab was associated with a [redacted] compared to docetaxel, indicated by a [redacted]. Additionally, as shown in Figure 5, there is considerable overlap between the 95% confidence intervals (CI) for the HRs for nivolumab versus docetaxel from the PD-L1 <1% and ≥1% subgroups, with the HR in the PD-L1 <1% subgroup located within the 95% CI of the PD-L1 ≥1% subgroup. As such there is not sufficient evidence that there is a statistically significant difference between these subgroups in terms of OS. Given the smaller sample size in the intended for docetaxel subgroups, the 95% CIs associated with the HRs are wider than for the all-randomised population. Additionally, there is also considerable overlap in the confidence intervals (CIs) of the HRs for the all-randomised population and indented for docetaxel subgroup for each of the subgroups analysed. As such there is not sufficient evidence to suggest a statistically significant difference between the all-randomised population and indented for docetaxel subgroup in terms of the treatment effect for OS for all patients or PD-L1 subgroups.

The results from each of the PD-L1 subgroups are presented as follows:

- Figure 6 and Figure 7, for Kaplan-Meier plots of OS in the PD-L1 <1% and PD-L1 ≥1% subgroups, respectively
- Table 10 for a summary of OS rates in the PD-L1 <1% and PD-L1 ≥1% subgroups
- Figure 8 and Figure 9, for Kaplan-Meier plots of PFS in the PD-L1 <1% and PD-L1 ≥1%, respectively
- Table 11 for a summary of PFS rates in the PD-L1 <1% and PD-L1 ≥1% subgroups
- Figure 10 and Figure 11, for Kaplan-Meier plots of TTD in the PD-L1 <1% and PD-L1 ≥1%, respectively
- Table 12 for a summary of TTD rates in the PD-L1 <1% and PD-L1 ≥1% subgroups

Table 9: Hazard ratio for OS, full population and PD-L1 subgroups for the all-randomised population and intended for docetaxel subgroup

Population		All-randomised population		Intended for docetaxel subgroup	
		Nivolumab	IC	Nivolumab	Docetaxel
All patients	n/N (%)	218/240 (90.8)	118/121 (97.5)	[redacted]	[redacted]
	HR (95% CI; p-value)[a]	0.6858 (0.5483, 0.8579; p<0.001)		[redacted]	
PD-L1 <1%	n/N (%)	72/76 (94.7)	40/40 (100)	[redacted]	[redacted]
	HR (95% CI; p-value)[a]	0.7429 (0.5015, 1.101; p=0.138)		[redacted]	
PD-L1 ≥1%	n/N (%)	87/96 (90.6)	60/61 (98.4)	[redacted]	[redacted]
	HR (95% CI; p-value)[a]	0.5397 (0.3857, 0.7554; p<0.001)		[redacted]	

[a] Computed using unstratified Cox proportional hazards model with treatment group as the sole covariate.
Abbreviations: CI: confidence interval; HR: hazard ratio; IC: investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Figure 5: Forest plot of hazard ratio for OS, full population and PD-L1 subgroups for the all-randomised population and intended for docetaxel subgroup

Abbreviations: OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Overall survival

Figure 6: Kaplan-Meier plot of overall survival for patients with the PD-L1 <1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Figure 7: Kaplan-Meier plot of overall survival for patients with the PD-L1 ≥1% in the intended for docetaxel subgroup of in CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 10: Summary of overall survival – PD-L1 subgroups in the intended for docetaxel subgroup

Subgroup/Outcome	Nivolumab	IC
PD-L1 <1%		
Deaths, n/N (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
PD-L1 ≥1%		
Deaths, n/N (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Progression-free survival

Figure 8: Kaplan-Meier plot of progression-free survival for patients with the PD-L1 <1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Figure 9: Kaplan-Meier plot of progression-free survival for patients with the PD-L1 ≥1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 11: Summary of progression-free survival – PD-L1 subgroups in the intended for docetaxel subgroup

Subgroup/Outcome	Nivolumab	IC
PD-L1 <1%		
Events, n/N (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
PD-L1 ≥1%		
Events, n/N (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; IC: investigator's choice; PD-L1: programmed death ligand 1; PFS: progression free survival.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Time to treatment discontinuation

Figure 10: Kaplan-Meier plot of time to treatment discontinuation for patients with the PD-L1 <1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: PD-L1: programmed death ligand 1.
Source: Bristol-Myers Squibb Data on File: CheckMate 141 (15th October 2019)[2]

Figure 11: Kaplan-Meier plot of time to treatment discontinuation for patients with the PD-L1 ≥1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 12: Summary of time to treatment discontinuation – PD-L1 subgroups in the intended for docetaxel subgroup

Subgroup/Outcome	Nivolumab	IC
PD-L1 <1%		
Events, n/N (%)	[redacted]	[redacted]
Median TTD, months (95% CI)	[redacted]	[redacted]
PD- L1 ≥1%		
Events, n/N (%)	[redacted]	[redacted]
Median TTD, months (95% CI)	[redacted]	[redacted]

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; IC: investigator's choice; PD-L1: programmed death ligand 1; TTD: time to treatment discontinuation.
Source: CheckMate 141 Data on File (15th October 2019)[2]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy (CDF review of TA490) [ID1585]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm** on **Friday 23 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol Myers Squibb Pharmaceuticals Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of the trial population to NHS clinical practice time horizon		ERG response
1. Is Checkmate 141 population generalisable to the UK population?	• Whilst there are small differences in baseline characteristics between CheckMate 141 and the systemic anti-cancer therapy (SACT) cohort, the results observed in CheckMate 141 can be considered generalisable to the UK population. Patients in the SACT cohort were slightly older than the patients in CheckMate 141 (median age of 62.0 versus 59.0 years, respectively). Additionally, the SACT cohort included 33 (7%) patients with Eastern Cooperative Oncology Group (ECOG) performance status 2–3, and 65 (13%) patients with missing ECOG status, suggesting that nivolumab has been used in line with the European Medicines Agency (EMA) licence in this indication, which does not exclude patients based on performance status. This is broader than the original inclusion criteria for entering the CDF, which was restricted to patients with ECOG status 0–1. Despite these differences, the generalisability of outcomes from CheckMate 141 to the UK population is supported by evidence from the SACT cohort, showing strikingly similar results for survival at 12 months, which was 34% in the SACT cohort compared to 33.4% in CheckMate 141. • In the SACT cohort, at 6 and 12 months, 28% and 17% of all patients respectively were still receiving treatment, compared to XX% and XXX% of patients in CheckMate 141. Whilst individuals in the SACT cohort had a longer median time to stopping treatment, this may be due to differences in timepoints for progression assessment between CheckMate 141 and the SACT cohort, as clinicians have suggested that patients in the UK receive a scan around 12 weeks after starting treatment to check for progression. Therefore, differences in median time to stopping treatment may not be due to differences between patient populations, and would be applicable to both treatment arms.	• The ERG acknowledges that the patients treated within the SACT data set do seem largely similar to those in CheckMate 141, apart from a higher ECOG performance status in the latter. It was stated in the ERG report that uncertainty in generalisability might be reduced by comparison between SACT and the docetaxel subgroup, which has been addressed in Question 2 below.
2. What is the most appropriate source of data	• The most appropriate source for assessing nivolumab's clinical and cost-effectiveness compared to docetaxel is the all-randomised population from CheckMate 141. Whilst docetaxel is considered to be the main comparator, feedback from a clinical expert consulted as part of this response suggests the majority of patients in UK clinical practice in this line of therapy would not receive	• The ToE specified that docetaxel should be the comparator. Therefore, the most appropriate evidence

for assessing nivolumab's clinical- and cost-effectiveness compared with docetaxel?
a. investigator's choice (IC) in the all-randomised population
b. the docetaxel subgroup (i.e. people who received docetaxel on the IC arm and who would have received docetaxel on the nivolumab arm)

docetaxel, and instead would receive no active treatment at all (i.e. palliative or best supportive care [BSC]). As a more tolerable treatment option, the introduction of nivolumab has allowed patients who would otherwise be unfit for docetaxel and have no remaining treatment options to receive an active treatment in this later line of therapy. Nivolumab is therefore used in a broader population in clinical practice than the patient population who are fit enough to receive docetaxel. Despite this, for completeness, and at the request of NICE and the ERG, the clinical effectiveness results have been provided for the patients in the CheckMate 141 'intended for docetaxel' subgroup.

- A summary of the baseline characteristics of patients included in the intended for docetaxel subgroup of CheckMate 141 versus the all-randomised population and the SACT data cohort study is presented in Table 1. There are clear similarities between the docetaxel only subgroup and the all-randomised population of the CheckMate 141 trial. [redacted] and patients had similar performance status: [redacted]% in the intended for docetaxel subgroup versus 20.4% in the all-randomised population had an ECOG score of 0, and [redacted]% versus 78.8% had an ECOG score of 1, respectively. The similarities in baseline characteristics suggest that the intended for docetaxel subgroup is no more or less generalisable to the SACT data cohort and thus UK clinical practice than the all-randomised population. Baseline characteristics for the docetaxel arm of the intended for docetaxel subgroup and the IC arm of the all-randomised population are presented in Appendix 1.

Table 1: Baseline characteristics of patients in the intended for docetaxel subgroup versus the Checkmate 141 trial and the SACT cohort study

Characteristic	CheckMate 141; Nivolumab (n=240)	CheckMate 141 (Intended for Docetaxel); Nivolumab (n=[redacted])	Characteristic	SACT data cohort study
Male, n (%)	197 (82.1)	[redacted]	Male, n (%)	411 (81)
Age, median (years)	59.0	[redacted]	Age, median (years)	62
Age categorisation, n (%)				

from the CheckMate 141 trials is those patients who would have been treated with docetaxel according to 'Investigator Choice' (IC) (docetaxel subgroup), some of whom were randomised to docetaxel and others to nivolumab. As stated in the ERG report: "Using the all-randomised data, including that from the whole IC arm implies equivalence between docetaxel and methotrexate, which the ToE explicitly rejects." The ERG would therefore argue that the best source of evidence for a comparison with docetaxel should be the subgroup of those chosen to receive docetaxel according to IC (docetaxel subgroup). " Of course, some patients might also be unsuitable for docetaxel. However, the ToE explicitly contrasted these patients with those who would be eligible for docetaxel. Therefore, stating that docetaxel was the main

<40	14 (6)	XXXXX	<40	15 (3)
40-49	18 (8)	XXXXX	40-49	39 (8)
50-59	90 (38)	XXXXXX	50-59	145 (29)
60-69	87 (36)	XXXXXX	60-69	194 (38)
70-79	29 (12)	XXXXXX	70-79	104 (21)
80+	2 (1)		80+	9 (2)
Performance status, n (%)				
0	49 (20.4)	XXXXXXXX	0	122 (24)
1	189 (78.8)	XXXXXXXX	1	286 (57)
≥2	1 (0.4)	X	2	29 (6)
			3	4 (1)
			4	0 (0)
Missing	1 (0.4)	X	Missing	65 (13)
PD-L1 score				
<1	76 (31.7)	XXXXXXXX	<1	55 (11)
≥1	96 (40.0)	XXXXXXXX	≥1	52 (10)
Can't be quantified	68 (28.3)	XXXXXXXX	Can't be quantified	189 (37)
			Not recorded	210 (42)

Abbreviations: PD-L1: programmed death ligand 1; SACT: Systemic Anti-Cancer Therapy.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Table 4.2-1-4.2-2[1], CheckMate 141 Data on File (15th October 2019),[2] Public Health England report[3]

- As acknowledged in the technical report, it is important to note that CheckMate 141 was not powered to detect differences between nivolumab and the individual therapies comprising IC; a comparison versus docetaxel alone therefore lacks the robustness of using the all-randomised IC population, in part due to the resulting small sample sizes. The all-randomised population includes 240 patients receiving nivolumab and 121 patients receiving IC, whereas the docetaxel subgroup includes only XX patients receiving nivolumab and XX patients receiving docetaxel. In addition, as discussed in the response to comparator implies that the patients not eligible for docetaxel are not of interest or at least of less interest. The ToE also stated that patients not eligible for docetaxel would probably receive methotrexate. This would imply that the most appropriate CheckMate 141 data would be from those patients who would have been treated with methotrexate according to IC 9methotrexate subgroup).
- It does appear that there is little difference in baseline characteristics between the all-randomised and the docetaxel subgroup.

	Question 3, the clinical outcomes for the intended for docetaxel subgroup are similar to the all-randomised population, with no statistically significant difference observed in the treatment effect for OS. As such, the all-randomised population is the most appropriate source of data for assessing nivolumab's clinical- and cost-effectiveness compared with docetaxel. • Although docetaxel is recognised as the primary comparator, the scope of the original appraisal and the eligibility criteria for the managed access agreement, which included patients who "would otherwise be potentially fit for docetaxel-based or methotrexate-based 2nd-line chemotherapy", acknowledges that patients may also receive methotrexate or another taxane (i.e. paclitaxel) in standard clinical practice. The conclusion made by the committee in the original TA490 appraisal was that "docetaxel would be the most appropriate comparator for people fit enough to have docetaxel" (TA490 FAD; Section 3.2), and so it would be remiss to only focus on patients intended for docetaxel given the expected use of nivolumab for patients who might otherwise receive something other than docetaxel. The Terms of Engagement also stipulate that the committee's preferred assumptions are not expected to change at the CDF review. • Patients in the SACT cohort may have had worse fitness than the patient population in CheckMate 141 (the SACT cohort included 33 (7%) patients with ECOG performance status 2–3), indicating that patients in clinical practice may be more likely to be unfit to receive docetaxel than the patients in CheckMate 141. • Based on feedback from a clinical expert consulted as part of this response, the majority of patients who are not able to tolerate docetaxel due to age, fitness or comorbidities may in fact receive no active treatment in clinical practice. The introduction of nivolumab has provided a safe and effective treatment option for these patients who would otherwise have received palliative care/BSC alone. • Clinical expert feedback indicated that the Kaplan-Meier plot of overall survival (OS) for the IC arm of the CheckMate 141 trial (as shown in Figure 1) was more generalisable to patients in UK clinical practice who would be eligible for nivolumab than the Kaplan-Meier plot for the intended for docetaxel subgroup. As such, the most appropriate source for assessing nivolumab's clinical and cost-effectiveness is the all-randomised population from CheckMate 141.	
3. Are clinical- and cost-effectiveness	• The results for OS, progression free survival (PFS), and time to treatment discontinuation (TTD) indicate that the clinical- and cost-effectiveness may be similar between the all-randomised population and the intended for docetaxel subgroup. However, as per the response to Question 2, the intended for docetaxel	• The ERG agrees with the company that the docetaxel subgroup seem to have had

results compared with docetaxel in the all-randomised population similar to results in the docetaxel subgroup	subgroup may not be fully reflective of the patients who are likely to receive nivolumab in clinical practice. Furthermore, the smaller sample size and lack of power means there is greater uncertainty and therefore the results for this subgroup should be interpreted with caution. Despite this, full analyses for the intended for docetaxel subgroup, including overall survival OS, PFS and TTD, as well as subgroup analyses based on PD-L1 status, are presented in Appendix 1. • The Kaplan-Meier plot of OS for the all-randomised population and the intended for docetaxel subgroup is presented in Figure 1. The Kaplan-Meier plots for both treatment arms [redacted]. A clinical expert confirmed that the divergence may be due to the relatively better fitness of the intended for docetaxel subgroup versus those in the IC arm as a whole, who are in fact more likely to be representative of patients in current clinical practice. The OS Hazard Ratios (HRs) for the all-randomised population and the intended for docetaxel subgroup are presented in Table 2. In both populations analysed, nivolumab was associated with a [redacted] compared to IC, indicated by a [redacted]. Given the smaller sample size of the intended for docetaxel subgroup, the 95% confidence intervals (CIs) associated with the HR are wider than for the all-randomised population. There is considerable overlap in the CIs of the HRs for the all-randomised population and intended for docetaxel subgroup, which means is not sufficient evidence for a statistically significant difference between these populations in terms of the treatment effect for OS. Therefore, the results could be considered similar between the two populations. In addition, results for PFS and TTD also appear to exhibit comparable trends to the all-randomised population (Appendix 1). As the clinical results can be considered similar across the two populations, it is more appropriate to use the all-randomised population for this appraisal, as it is adequately powered to detect differences between treatment arms and is most reflective of patients in this indication. • In the intended for docetaxel subgroup, [redacted] patients had PD-L1 <1% ([redacted] received nivolumab and [redacted] received docetaxel) and [redacted] had PD-L1 ≥1% ([redacted] received nivolumab and [redacted] received docetaxel). Given the extremely small numbers of patients in each treatment arm within these subgroups, as well as the risk of selection bias due to broken randomisation, the results for these subgroups are subject to high degree of uncertainty and not used for decision-making. However, the clinical results have been presented in Appendix 1 for completeness.	a better prognosis than all randomised population. It does appear that the treatment effect of nivolumab is slightly less (HR higher) for the docetaxel subgroup, although this is uncertain.

Figure 1: Kaplan-Meier plot of OS with nivolumab versus IC, all-randomised population and intended for docetaxel subgroup

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval, OS: overall survival, IC: investigators choice, KM: Kaplan Meier
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 2: Hazard ratio for OS with nivolumab versus IC, all-randomised population and intended for docetaxel subgroup

Population	HR for OS (95% CI; p-value)[a]
All-randomised population, versus IC	0.6858 (0.5483, 0.8579; p<0.001)
Intended for docetaxel, versus docetaxel	[redacted]

[a] Computed using unstratified Cox proportional hazards model with treatment group as the sole covariate.
Abbreviations: CI: confidence interval; HR: hazard ratio; IC: investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

- A cost-effectiveness analysis where OS, PFS and TTD data are based on the intended for docetaxel subgroup of the CheckMate-141 trial has been conducted, and the results of the analysis are presented in Table 3. All assumptions were in line with the base case analysis (as reported in Table 16 of the original evidence submission). This scenario produced a similar ICER versus docetaxel than the base case analysis (an increase of £4,442 from £37,257) but is still cost-effective. These results demonstrate that, despite the considerable uncertainty with using data from the intended for docetaxel subgroup due to the small sample size and lack of power, nivolumab is a cost-effective use of NHS resources.
- Given the high degree of uncertainty in the clinical data for the PD-L1 subgroups of the intended for docetaxel subgroup, cost-effectiveness analyses based on these data were not explored.

Table 3: Intended for docetaxel scenario analysis (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	11,213	0.85	0.46	[redacted]	0.56	[redacted]	41,695

Please note that these results include the ERG's correction to docetaxel dose intensity.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG: life years gained; PAS: Patient Access Scheme; QALYs, quality-adjusted life years.

Issue 2: Extrapolation of overall survival		
4. What is the most appropriate method for extrapolating overall survival (OS) data in the 'all-randomised' population?	• As reported in the original evidence submission, the committee-preferred assumption of a piecewise approach has been used in the company base case. The lognormal distribution provided a better visual fit to the observed trial data compared to the exponential distribution when considering the committee-preferred piecewise models in TA490, and the 96-week cut-off point was selected to maximise the use of the observed trial data. These assumptions were confirmed as the most plausible by a clinical expert who was consulted as part of this response. BMS appreciate the ERG and NICE technical team's agreement with the company approach to modelling OS. • BMS also acknowledge that fully parametric models may provide plausible alternatives for extrapolating OS, and scenarios exploring the fully parametric lognormal and loglogistic extrapolation for OS were	• See ERG report section 4.1.5: "the ERG would, based on the AIC, agree with the log-normal distribution to extrapolate OS using the piecewise model with a 96-week cut off. However, it should be noted that the selection of the approach to

presented as part of the original submission. In these scenarios, the ICERs versus docetaxel were similar to the base case analysis (all within £4,000), and all were less than £50,000 per QALY gained.

- The proportion of patients alive at all timepoints was also similar across these three extrapolation methods for both treatment arms (within 1% at the majority of timepoints), as well as matching the available Kaplan-Meier data from the CheckMate-141 trial, as shown in Table 4. Ultimately, whilst the fully parametric models produced similar results, the piecewise log-normal is in line with the committee-preferred assumptions from TA490, and is therefore the preferred choice for the base case.

Table 4: Comparison of OS (%) using different extrapolation methods, for both treatment arms

Extrapolation model, years	1	2	3	4	5	10	15	20	25
Nivolumab									
CheckMate 141 (Kaplan-Meier data)	33.4	16.8	10.3	8.0	n/a	n/a	n/a	n/a	n/a
Piecewise, lognormal, 96-week (base-case)	33.4	16.1	10.1	7.3	5.7	2.6	1.5	1.0	0.8
Fully parametric, lognormal	33.6	17.3	10.6	7.2	5.2	1.6	0.7	0.4	0.2
Fully parametric, loglogistic	32.7	16.5	10.5	7.4	5.7	2.4	1.4	1.0	0.7
Investigator's choice (IC)									
CheckMate 141 (Kaplan-Meier data)	19.4	5.9	2.5	1.7	n/a	n/a	n/a	n/a	n/a
Piecewise, lognormal, 96-week (base-case)	19.4	5.6	2.3	1.1	0.6	0.1	0.0	0.0	0.0
Fully parametric, lognormal	18.9	5.5	2.2	1.0	0.6	0.1	0.0	0.0	0.0
Fully parametric, loglogistic	17.6	5.7	2.8	1.7	1.1	0.3	0.2	0.1	0.1

Abbreviations: OS: overall survival; PFS: progression-free survival
Source: Company's model ("OS" tab)

extrapolate OS is not informed by external validation (neither expert opinion nor external data) of the extrapolated OS. Hence, the plausibility of the extrapolated OS might be considered uncertain."

"Although the committee clearly indicated that a piecewise model is expected to be used to extrapolate OS, the ERG agrees with the company that fully parametric models are still considered to provide plausible alternative to extrapolate OS."

Issue 3: Time to treatment discontinuation		
5. What is the most appropriate method for	• For nivolumab, the 2-spline normal model provided the best statistical fit and a reasonable visual fit to the observed data, and was thus considered to be more plausible for extrapolation of TTD than the generalised gamma model used in TA490. The 2-spline model also predicted a reasonable estimate of mean TTD when compared to PFS (i.e. mean TTD and mean PFS were similar). As such, the 2-spline normal model was considered to be the most appropriate extrapolation method for nivolumab. For IC.	• See ERG report section 4.1.5, particularly noting the third point:

extrapolating time on treatment with (a) nivolumab and (b) docetaxel alone?	[redacted] in the CheckMate 141 trial, thus, [redacted] These assumptions were confirmed as the most plausible by a clinical expert consulted as part of this response. BMS appreciate the NICE technical team's agreement with the company approach to modelling time to discontinuation (TTD). • The use of TTD data from the SACT cohort for the cost-effectiveness model was explored as part of the response to the ERG clarification questions. The observed TTD for nivolumab in the SACT cohort was generally higher than the CheckMate 141 trial, as shown in the company evidence submission. The use of TTD data from the SACT cohort in the cost-effectiveness analysis therefore produced a higher estimate of the ICER than the base case analysis (i.e. using data from CheckMate 141) due to the increased costs related to treatment that were accrued in the nivolumab arm. In this analysis, uncertainty in the long-term extrapolation of TTD was largely mitigated by the inclusion of the 2-year stopping rule, and so the relative immaturity of the SACT TTD data was less of a concern. However, in a scenario where a stopping rule is not applied, the relative immaturity of the SACT TTD data would introduce considerable uncertainty in the long-term extrapolation of TTD. • Additionally, the SACT cohort does not include patients receiving IC, so cannot inform TTD for the comparator arm. As per the response to Question 1, the higher TTD observed for individuals in the SACT cohort may have been due to differences between the CheckMate 141 trial and the SACT cohort with respect to the timepoints for progression assessment, as clinicians have suggested that patients in the UK receive a scan around 12 weeks after starting treatment to check for progression (regardless of the treatment given). As such, a higher TTD may be expected in clinical practice than observed in CheckMate 141 for patients currently receiving IC. Therefore, as per the technical report, BMS agree that it would be inappropriate to use the SACT cohort TTD data to inform model parameters for nivolumab, since this would be inconsistent with the source of TTD data for IC, as well as OS and PFS data.	"The generalised gamma distribution was the preferred distribution to model TTD in TA490 and, according to the ERG, there is no clear justification to deviate from this. Additionally, the ERG prefers not to use the [redacted] as 1) it might overfit the CheckMate 141 trial data which seems suboptimal for decision-making in UK clinical practice (i.e. generalisability might be limited); 2) the tail of the [redacted] might be very uncertain, if many patients are censored a single event might already have a substantial impact on the curve and; 3) using the [redacted] for one treatment while using parametric survival curves for the other treatment might introduce bias (i.e. difference between treatments due to inconsistency in the methods used). Given the above, the ERG preferred to use the generalised gamma distribution to estimate

		TTD (for both nivolumab and IC) in the ERG base-case.''
Issue 4: Stopping rule and duration of treatment effect		
6. Is a 2-year stopping rule for nivolumab appropriate?	• A stopping rule was included in the base case analysis of the company evidence submission. The use of a stopping rule in routine clinical practice was considered to be acceptable by clinicians consulted as part of TA490 (FAD Committee Papers 2 and 3; Comments on the ACD) and also NHS England (ACD Committee Papers 5; NHS England statement). Furthermore, based on the TTD extrapolation used in the base case, [redacted] of patients were predicted to still be receiving nivolumab after two years of treatment. Additionally, the incorporation of a two-year stopping rule was shown to be feasible during the CDF data collection phase. • Stopping rules have been accepted for nivolumab in other indications. In TA484, the committee considered that it was biologically plausible that the effects of nivolumab might continue after treatment stops, although the exact continued effect was uncertain. The committee noted comments on the appraisal consultation documents made by NHS England and other consultees that a 2-year stopping rule was acceptable to both patients and clinicians and would be implementable. The committee therefore accepted the stopping rule, despite the fact that no stopping rule was applied in the pivotal clinical trial (CheckMate 037).[4] More recently, a stopping rule was accepted in TA655, which is indicated for a similar tumour type (metastatic squamous non-small-cell lung cancer [NSCLC]).[5] • A stopping rule has also recently been accepted in a NICE appraisal of pembrolizumab in a similar SCCHN indication (untreated metastatic or unresectable recurrent SCCHN; ID1140).[6] • Based on the arguments above, BMS believes a stopping rule is appropriate for nivolumab.	• See ERG report section 4.1.8: "The company incorporated a 2-year stopping rule to nivolumab. However, according to the ToE, the committee considered analyses without a stopping rule as more appropriate for decision-making. Moreover, excluding the 2-year stopping rule is consistent with the CheckMate 141 trial data used to estimate effectiveness. The justification by the company to include the stopping rule is minimal (i.e. that [redacted], and a 2-year stopping rule has been shown to be clinically plausible during the CDF data collection period). Therefore, the ERG excluded the 2-year stopping rule in its base-case"

		• It should be noted that, if an treatment stopping rule is adopted this might have implications for treatment waning assumptions. (as highlighted in ERG report section 4.1.5).
7. If nivolumab is given for 2 years and then stopped, is it clinically plausible that its treatment benefit would continue for a lifetime?	• Nivolumab has an innovative mechanism of action, blocking PD-1 on T cells, thus promoting long term anti-tumour immunity by stimulating the immune system, rather than targeting cancer cells directly. Accumulating evidence suggests that treatment with PD-L1 inhibitors such as nivolumab may facilitate longer term benefit following treatment discontinuation. • A two-year stopping rule was implemented in KeyNote-010, a Phase III randomised trial for pembrolizumab versus docetaxel in participants with previously treated, PD-L1-positive, advanced non-small cell lung cancer (NSCLC). Of the 47 patients that completed two years of treatment, only two patients (4%) experienced progression.[7] • A pooled analysis of Phase II and III studies by Schadendorf *et al.* (2017) sought to measure the efficacy and safety of nivolumab plus ipilimumab in patients with advanced melanoma who discontinued treatment because of adverse events (AEs). Efficacy outcomes appeared similar between patients who discontinued treatment due to experiencing AEs during the induction phase and those who did not discontinue due to AEs. At a minimum follow-up of 18 months, median PFS was 8.4 months for patients who discontinued versus 10.8 months for those who did discontinue. Furthermore, the ORR in discontinuers was 58.3% versus 50.2% in those that did not discontinue.[8] These results demonstrate that even after discontinuation, many patients may continue to derive benefit from PD-L1 inhibitors. • A dose escalation study (CA209003) evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumours incorporated a two-year stopping rule. Sixteen patients with NSCLC discontinued nivolumab after two years of treatment. Of these patients, 12 remained alive and progression free without the need for subsequent therapy.[9] • In line with PD-L1 inhibitors in other indications, of the 13 patients in the nivolumab arm of the CheckMate 141 trial who were alive and in follow-up, [redacted]	• See ERG report section 4.1.5: "the (smoothed) hazard rate of nivolumab and IC seem to converge (indicating similar mortality probabilities for both treatments, see clarification response Figure 2), this converging trend might potentially occur earlier if continued nivolumab treatment after 2 year was not allowed in the CheckMate 141 trial (i.e. if the 2-year stopping rule for nivolumab was reflected in the clinical data)." • In response to the next point, the company "acknowledge that smoothed hazards from CheckMate 141 appear to converge after approximately 52 months, which may indicate that the

	[redacted], demonstrating the durability of the survival benefit associated with nivolumab after treatment discontinuation.[2] • Therefore, based on the arguments above, it is appropriate to assume that treatment benefit will continue in patients who discontinue nivolumab after two years.	nivolumab treatment effect may last for additional 3 years after stopping treatment (up to 5 years in total).” As mentioned above, the point of convergence might be earlier if a stopping rule is implemented. • The evidence from other treatments, albeit also PD-L1 inhibitors, provides little validation for the prediction of outcomes with nivolumab, particularly given the difference in populations. The evidence of the OS of the patients who had discontinued treatment in the CheckMate 141 trial does not provide validation for the continued benefit of nivolumab following the implementation of a stopping rule at an arbitrary time point. This is because, although some patients might survive for a substantial period after discontinuing nivolumab, this is probably a selected subgroup of patients. Only some of these patients will

		have discontinued before 2 years i.e. when the stopping rule would be applied. The remainder might still have been on treatment at 2 years and forced to stop in accordance with the stopping rule and thus would be prevented from receiving any continued benefit from nivolumab post-2 years. These also do not include the patients who would not have survived much longer than 2 years, but still longer than they would have done if treatment had not been curtailed at 2 years due to the stopping rule.
8. If nivolumab is given for 2 years and then stopped, is it clinically plausible that its treatment benefit would continue for 3 further years (i.e. 5 years in	• As per the response to Question 7, there is accumulating evidence to suggest that treatment with PD-L1 inhibitors, including nivolumab, may facilitate longer term benefit even following treatment discontinuation. • As reported in the original submission, inspection of the log cumulative hazards plot showed that towards the end of the observed follow-up period for CheckMate 141 there was a difference between treatment arms in the change in hazards over time, with a reduction in the hazard over time in the nivolumab arm and a relatively constant hazard in the IC arm. Should this trend continue beyond the 4-year follow-up period, it would not be appropriate to assume that the hazard in the nivolumab arm becomes equal to the IC arm. However, BMS acknowledge that smoothed hazards from CheckMate 141 appear to converge after approximately 52 months, which may indicate that the nivolumab treatment effect may last for additional 3 years after stopping treatment (up to 5 years in total).	• See previous comment

total, the TA490 committee's preferred assumption)?	• To reflect the possibility that some patients treated with nivolumab may maintain improvements in survival beyond the timepoints used in the treatment waning scenarios (5, 7 and 10 years), analyses were also conducted in which the treatment waning effect (i.e. setting the probability of death to be the same as IC) was only applied to a proportion of patients, with the remaining patients having survival modelled based on the chosen extrapolation. In these "partial" treatment waning scenarios, the proportion of patients for whom the treatment waning effect was not applied was based on the proportion of patients in CheckMate 141 who achieved a best overall response of complete response, partial response or stable disease (XXXX%). As per the response to Question 7, some patients receiving nivolumab experience a durable response, which is expected to result in longer term benefit even following treatment discontinuation. Across all three scenarios, ICERs were similar to the base case (as shown in Table 22 of the original submission).	
Issue 5: Utility values		
9. Which approach to utility values is most appropriate? a. Treatment-dependent versus treatment-independent utility values b. incorporating decrease in utility values before death (or not)	• The treatment-specific utility values for PF and PD have been used in the revised base case analysis to reflect the benefits in health-related quality of life (HRQoL) that are provided with nivolumab, as was recognised by clinical experts consulted as part of TA490. These utility values were derived from EQ-5D data collected during the CheckMate 141 trial and demonstrate the improved utility post-progression for patients who were randomised to receive nivolumab versus IC. The mixed model that included progression status and treatment arm (used to derive treatment-specific utility values) was associated with a better statistical fit than the model including progression status alone (treatment-independent utility values). Therefore, the treatment-dependent model should be used as the base case for decision-making. • Clinical expert feedback sought as part of this response suggested that patients who remain on nivolumab for more than a few months and respond well to treatment are more likely to experience a utility benefit post-progression. Therefore, whilst it is recognised that some patients receiving nivolumab may discontinue treatment or progress quickly (and therefore may be expected to have similar utility post-progression to patients who receive IC), the true utility values for the cohort as a whole are likely to lie closer to treatment-dependent than to treatment-independent values. • Given the differences between the nivolumab and IC arms in the number of EQ-5D observations, particularly post-progression (n=XXX for nivolumab and n=XX for IC), the treatment-independent utility	• See ERG report section 4.1.7: a. Treatment-dependent versus treatment-independent utility values "In the ToE it was stated that the most appropriate utility values lie between the treatment-dependent (regression model 6) and the treatment-independent (regression model 7) estimates. It is noteworthy that in one of the TA490 ERG addenda, the ERG explored the use of a disutility of XXXXX (difference in post progression utility between nivolumab and IC) for patients

	values are mainly driven by the experiences of patients in the nivolumab treatment arm. As well as failing to account for potential differences between treatment arms, these values are therefore also not considered to be an accurate reflection of the utility of patients who receive IC. • In order to address the concerns raised in TA490 about utility remaining constant over time, the economic model submitted as part of the original evidence submission includes the option to apply decrements in utility based on time to death. Specifically, utility decrements can be applied for the proportion of patients who are predicted to die within the next three model cycles, with separate decrements applied based on whether patients are one (0–28 days), two (29–56 days) or three (57–84 days) cycles from death. When these decrements are applied, patients in the nivolumab arm who are in the progressed disease state are initially assumed to have improved utility compared to patients in the IC arm, but as they patients approach death they experience worsening utility. It is also assumed that utility prior to death is the same regardless of treatment arm (i.e. decrements applied to the nivolumab arm were larger than those applied to the IC arm, as shown in Table 15 of the original evidence submission, such that patients experienced treatment-independent utility prior to death). The resulting ICER lies between the ICERs produced when treatment-dependent and treatment-independent utility values are applied individually. • A number of prior NICE appraisals for cancer immunotherapies have accepted the use of time-to-death utility values. Examples include ipilimumab for previously untreated advanced melanoma (TA319) and pembrolizumab for untreated metastatic squamous non-small-cell lung cancer (TA600).[10, 11] Notably, a previous submission for nivolumab for advanced melanoma (TA384) also included time-to-death utility values.[12] • Based on the arguments above, BMS believe that the most plausible approach is to use the treatment-dependent utility values with decrements applied based on time to death.	that discontinued nivolumab treatment as an alternative scenario (i.e. assuming treatment independent utility values after treatment discontinuation). Also, in this addenda, the ERG wondered why the company did not opt to use regression Model 1 or Model 2 (adding a covariate for being off treatment), given the lower AIC. These models indicate the post-progression utility difference between the two treatments of XXXXX is potentially an overestimation given that this is XXXXX when considering the model with the lowest AIC." b. incorporating decrease in utility values before death "In the ToE for CDF review NICE stated that it expected the quality of life benefit to not remain constant over time and that the appropriate utility values should be reviewed in light of any new evidence. The company tried to address this by applying

		decrements in utility based on the proportion of patients who are predicted to die within the next three model cycles (so last three months only). Whilst this approach may account, to some extent, for decreasing health state utilities over time (see CS Table 15), according to the ERG this does not address the committee's concerns regarding the nivolumab quality of life (treatment) over time. According to the ERG, it would have been more intuitive to use time since start/ stop treatment (rather than time to death) to address this concern. In the PD state patients in the nivolumab arm have a large treatment benefit compared to patients in the IC arm (XXXX utility difference). As stated in the ERG report for TA490 (and highlighted above), the ERG wonders why the company did not opt to use a regression in which a covariate for being off treatment was added. This could then in turn be used for patients that discontinued nivolumab

		treatment (i.e. assuming treatment independent utility values after treatment discontinuation), as done in regression Model 1 or Model 2 (which had a better AIC than the currently used regression models). This would remove the constant quality of life benefit of treatment over time, which would have addressed the concerns highlighted in the ToE."
Issue 6: PD-L1 expression subgroups		
10. Does clinical- and cost-effectiveness of nivolumab vary by PD-L1 expression status?	• The clinical effectiveness results by PD-L1 status should be interpreted with caution, as CheckMate 141 was not powered to detect a difference between treatment arms in these subgroups. The overlap between the 95% CI of HRs for nivolumab versus IC in each of the PD-L1 subgroups demonstrates that there is no statistically significant difference between the subgroups in the treatment effect on OS. The HRs themselves do indicate that treatment with nivolumab is of benefit versus standard of care, regardless of PD-L1 status. • BMS believe that the evidence is such that the all-randomised population should be considered as the patient population within the CDF review. The implications of providing a recommendation based on PD-L1 status would mean patients who would benefit from treatment are denied access (either due to inconclusive tests [as demonstrated in the SACT cohort, where 79% of patients had missing or inconclusive PD-L1 data], or due to the occurrence of false negatives). This may introduce equity issues based on availability of testing.	• The ERG agrees that the PD-L1 status results need to be interpreted with caution. However, based on this evidence it does appear that PL-L1 status does affect the effectiveness of nivolumab and more so in the docetaxel subgroup, as shown by a larger difference in HRs between PD-L1 <1% and ≥1%. Similarly, the cost-effectiveness range, estimated by the ERG, differs for the subgroups

		based on PD-L1 status. It should however be noted that these subgroup analyses did not incorporate any additional costs related to PD-L1 which would be required if PD-L1 testing is not part of UK clinical practice.

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Appendix 1 – Clinical evidence for the docetaxel subgroup

The results for the intended for docetaxel subgroup (i.e. people who received docetaxel on the IC arm and who would have received docetaxel on the nivolumab arm) from the latest data cut of the CheckMate 141 trial (15th October 2019) (OS, PFS and TTD) are provided below. CheckMate 141 was not powered to detect differences between nivolumab and the individual therapies comprising IC. As such, the results of the following analyses should be interpreted with caution.

The baseline characteristics of the all-randomised population and the intended for docetaxel subgroup are presented in Table 5. In the nivolumab arms, [redacted] and patients had similar performance status: [redacted]% patients in the intended for docetaxel subgroup versus 20.4% in the all-randomised population had an ECOG score of 0, and [redacted]% versus 78.8% had an ECOG score of 1, respectively. Similarly, median age was [redacted]. Patients also had similar performance status: [redacted]% patients in the docetaxel arm versus 19.0% in the IC arm had an ECOG score of 0, and [redacted]% versus 77.7% had an ECOG score of 1, respectively.

Table 5: Baseline characteristics of patients in the intended for docetaxel subgroup versus the Checkmate 141 trial and the SACT cohort

Characteristic	CheckMate 141; Nivolumab (n=240)	CheckMate 141; IC (n=121)	CheckMate 141 (Intended for Docetaxel); Nivolumab (n=XX)	CheckMate 141 (Intended for Docetaxel); Docetaxel (n=XX)	Characteristic	SACT data cohort study
Male, n (%)	197 (82.1)	103 (85.1)	[redacted]	[redacted]	Male, n (%)	411 (81)
Age, median (years)	59.0	61.0	[redacted]	[redacted]	Age, median (years)	62
Age categorisation, n (%)						
<40	14 (6)	8 (7)	[redacted]	[redacted]	<40	15 (3)
40-49	18 (8)	14 (12)	[redacted]	[redacted]	40-49	39 (8)
50-59	90 (38)	35 (29)	[redacted]	[redacted]	50-59	145 (29)
60-69	87 (36)	41 (34)	[redacted]	[redacted]	60-69	194 (38)
70-79	29 (12)	23 (19)	[redacted]	[redacted]	70-79	104 (21)
80+	2 (1)	0 (0)			80+	9 (2)
Performance status, n (%)						
0	49 (20.4)	23 (19.0)	[redacted]	[redacted]	0	122 (24)
1	189 (78.8)	94 (77.7)	[redacted]	[redacted]	1	286 (57)
≥2	1 (0.4)	3 (2.5)	[redacted]	[redacted]	2	29 (6)
					3	4 (1)
					4	0 (0)
Missing	1 (0.4)	1 (0.8)	[redacted]	[redacted]	Missing	65 (13)
PD-L1 score						
<1	76 (31.7)	61 (50.4)	[redacted]	[redacted]	<1	55 (11)
≥1	96 (40.0)	40 (33.1)	[redacted]	[redacted]	≥1	52 (10)
Can't be quantified	68 (28.3)	20 (16.5)	[redacted]	[redacted]	Can't be quantified	189 (37)
					Not recorded	210 (42)

Abbreviations: PD-L1: programmed death ligand 1; SACT: Systemic Anti-Cancer Therapy.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Table 4.2-1-4.2-2[1], CheckMate 141 Data on File (15th October 2019),[2] Public Health England report[3]

Overall survival

The Kaplan-Meier plot of OS for the intended for docetaxel subgroup of the CheckMate 141 trial (15th October 2019) is presented in Figure 2. As shown in Table 6, the [redacted] at the time of the latest data cut of the CheckMate 141 trial. The [redacted] associated with nivolumab can also be seen in the Kaplan-Meier curves, which show a [redacted]. These additional data from the latest data cut of the CheckMate 141 trial clearly demonstrate that, as for the all-randomised population, [redacted] compared to the docetaxel subgroup.

Figure 2: Kaplan-Meier plot of overall survival in the intended for docetaxel subgroup of CheckMate 141

Data cut-off: 15th October 2019
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 6: Summary of overall survival – intended for docetaxel subgroup

Outcome	Data cut-off: 15th October 2019	
	Nivolumab (n=[redacted])	Docetaxel (n=[redacted])
Deaths, n/N (%)	[redacted])	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
12-month survival rate, % (95% CI)	[redacted]	[redacted]
18-month survival rate, % (95% CI)	[redacted]	[redacted]
24-month survival rate, % (95% CI)	[redacted]	[redacted]
36-month survival rate, % (95% CI)	[redacted]	[redacted]
48-month survival rate, % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IC: investigator's choice; NA: not applicable; OS: overall survival.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Progression-free survival

The Kaplan-Meier plot of PFS for the intended for docetaxel subgroup from the latest data cut is presented in Figure 3. A summary of PFS for the intended for docetaxel subgroup of the CheckMate 141 trial (15th October 2019) is presented in Table 7. As per the all-randomised population, [redacted]). However, as shown in Figure 3, there [redacted] and [redacted]. As shown in Table 7 and the Kaplan-Meier curves, the [redacted], in terms of [redacted], also [redacted], with a [redacted].

Figure 3: Kaplan-Meier plot of progression-free survival in the intended for docetaxel subgroup in CheckMate 141

Data cut-off: 15th October 2019
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 7: Summary of progression-free survival – intended for docetaxel subgroup

Outcome	Data cut-off: 15th October 2019	
	Nivolumab (n=XX)	IC (n=XX)
Events, n/N (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
6-month PFS rate, % (95% CI)	[redacted]	[redacted]
12-month PFS rate, % (95% CI)	[redacted]	[redacted]
18-month PFS rate, % (95% CI)	[redacted]	[redacted]
24-month PFS rate, % (95% CI)	[redacted]	[redacted]
36-month PFS rate, % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; IC: investigator's choice; NA: not applicable; PFS: progression free survival.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Time to treatment discontinuation

A summary of TTD for the intended for docetaxel subgroup of the CheckMate 141 trial (15th October 2019) is presented in Table 8. The Kaplan-Meier plot of TTD for the intended for docetaxel subgroup from the latest data cut is presented in in Figure 4. As for the all-randomised population, whilst median TTD is similar between the nivolumab and docetaxel arms (XXXX months [95% CI, XXXX, XXXX] for nivolumab versus XXXX months [95% CI, XXXX, XXXX] for IC), there is separation of the Kaplan-Meier curves from approximately X months.

Figure 4: Kaplan-Meier plot of time to treatment discontinuation in the all-randomised population in CheckMate 141

Data cut-off: 15th October 2019
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 8: Summary of time to treatment discontinuation – intended for docetaxel subgroup

Outcome	Data cut-off: 15th October 2019	
	Nivolumab (n=88)	IC (n=52)
Events, n/N (%)	XXXXXXXXXXX	XXXXXXXXXXXX
Median TTD, months (95% CI)	XXXXXXXXXXXXXXX	XXXXXXXXXXXXXXX

Abbreviations: CI: confidence interval; IC: investigator's choice; TTD: time to treatment discontinuation.
Source: CheckMate 141 Clinical Study Report Addendum (17th November 2016) Figure 5.1-1,[1] CheckMate 141 Data on File (15th October 2019)[2]

Results from the PD-L1 subgroups (<1% and ≥1%)

CheckMate 141 was not powered to detect differences between treatment arms in the different PD-L1 patient subgroups of the all-randomised population, nor to detect differences between nivolumab and the individual therapies comprising IC. Due to the resulting small sample sizes, the results of these subgroup analyses should be interpreted with considerable caution.

The hazard ratios (HRs) for OS for the intended for docetaxel subgroup from the latest data cut (15th October 2019) are presented in Table 9. In each of the populations analysed (full population or PD-L1 subgroups), nivolumab was associated with a [redacted] compared to docetaxel, indicated by a [redacted]. Additionally, as shown in Figure 5, there is considerable overlap between the 95% confidence intervals (CI) for the HRs for nivolumab versus docetaxel from the PD-L1 <1% and ≥1% subgroups, with the HR in the PD-L1 <1% subgroup located within the 95% CI of the PD-L1 ≥1% subgroup. As such there is not sufficient evidence that there is a statistically significant difference between these subgroups in terms of OS. Given the smaller sample size in the intended for docetaxel subgroups, the 95% CIs associated with the HRs are wider than for the all-randomised population. Additionally, there is also considerable overlap in the confidence intervals (CIs) of the HRs for the all-randomised population and indented for docetaxel subgroup for each of the subgroups analysed. As such there is not sufficient evidence to suggest a statistically significant difference between the all-randomised population and indented for docetaxel subgroup in terms of the treatment effect for OS for all patients or PD-L1 subgroups.

The results from each of the PD-L1 subgroups are presented as follows:

- Figure 6 and Figure 7, for Kaplan-Meier plots of OS in the PD-L1 <1% and PD-L1 ≥1% subgroups, respectively
- Table 10 for a summary of OS rates in the PD-L1 <1% and PD-L1 ≥1% subgroups
- Figure 8 and Figure 9, for Kaplan-Meier plots of PFS in the PD-L1 <1% and PD-L1 ≥1%, respectively
- Table 11 for a summary of PFS rates in the PD-L1 <1% and PD-L1 ≥1% subgroups
- Figure 10 and Figure 11, for Kaplan-Meier plots of TTD in the PD-L1 <1% and PD-L1 ≥1%, respectively
- Table 12 for a summary of TTD rates in the PD-L1 <1% and PD-L1 ≥1% subgroups

Table 9: Hazard ratio for OS, full population and PD-L1 subgroups for the all-randomised population and intended for docetaxel subgroup

Population		All-randomised population		Intended for docetaxel subgroup	
		Nivolumab	IC	Nivolumab	Docetaxel
All patients	n/N (%)	218/240 (90.8)	118/121 (97.5)	[redacted]	[redacted]
	HR (95% CI; p-value)[a]	0.6858 (0.5483, 0.8579; p<0.001)		[redacted]	
PD-L1 <1%	n/N (%)	72/76 (94.7)	40/40 (100)	[redacted]	[redacted]
	HR (95% CI; p-value)[a]	0.7429 (0.5015, 1.101; p=0.138)		[redacted]	
PD-L1 ≥1%	n/N (%)	87/96 (90.6)	60/61 (98.4)	[redacted]	[redacted]
	HR (95% CI; p-value)[a]	0.5397 (0.3857, 0.7554; p<0.001)		[redacted]	

[a] Computed using unstratified Cox proportional hazards model with treatment group as the sole covariate.
Abbreviations: CI: confidence interval; HR: hazard ratio; IC: investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Figure 5: Forest plot of hazard ratio for OS, full population and PD-L1 subgroups for the all-randomised population and intended for docetaxel subgroup

Abbreviations: OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Overall survival

Figure 6: Kaplan-Meier plot of overall survival for patients with the PD-L1 <1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Figure 7: Kaplan-Meier plot of overall survival for patients with the PD-L1 ≥1% in the intended for docetaxel subgroup of in CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 10: Summary of overall survival – PD-L1 subgroups in the intended for docetaxel subgroup

Subgroup/Outcome	Nivolumab	IC
PD-L1 <1%		
Deaths, n/N (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
PD-L1 ≥1%		
Deaths, n/N (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; investigator's choice; OS: overall survival; PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Progression-free survival

Figure 8: Kaplan-Meier plot of progression-free survival for patients with the PD-L1 <1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Figure 9: Kaplan-Meier plot of progression-free survival for patients with the PD-L1 ≥1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 11: Summary of progression-free survival – PD-L1 subgroups in the intended for docetaxel subgroup

Subgroup/Outcome	Nivolumab	IC
PD-L1 <1%		
Events, n/N (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
PD-L1 ≥1%		
Events, n/N (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; IC: investigator's choice; PD-L1: programmed death ligand 1; PFS: progression free survival.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Time to treatment discontinuation

Figure 10: Kaplan-Meier plot of time to treatment discontinuation for patients with the PD-L1 <1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: PD-L1: programmed death ligand 1.
Source: Bristol-Myers Squibb Data on File: CheckMate 141 (15th October 2019)[2]

Figure 11: Kaplan-Meier plot of time to treatment discontinuation for patients with the PD-L1 ≥1% in the intended for docetaxel subgroup of CheckMate 141

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: PD-L1: programmed death ligand 1.
Source: CheckMate 141 Data on File (15th October 2019)[2]

Table 12: Summary of time to treatment discontinuation – PD-L1 subgroups in the intended for docetaxel subgroup

Subgroup/Outcome	Nivolumab	IC
PD-L1 <1%		
Events, n/N (%)	[redacted]	[redacted]
Median TTD, months (95% CI)	[redacted]	[redacted]
PD- L1 ≥1%		
Events, n/N (%)	[redacted]	[redacted]
Median TTD, months (95% CI)	[redacted]	[redacted]

CheckMate 141 data cut-off: 15th October 2019
Abbreviations: CI: confidence interval; IC: investigator's choice; PD-L1: programmed death ligand 1; TTD: time to treatment discontinuation.
Source: CheckMate 141 Data on File (15th October 2019)[2]