NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Bristol-Myers Squibb (BMS)
   - Royal College of Pathologists

2. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Anthony Kong, clinical expert, nominated by the Royal College of Physicians

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

5. **BMS additional evidence submitted in response to ACD**
   - Additional evidence
   - Updated PAS analyses

6. **Review of BMS additional evidence** from Kleijnen Systematic Reviews

7. **Critique of revised PAS results from** Kleijnen Systematic Reviews

8. **Evidence provided by BMS:**
   - use of nivolumab in the Cancer Drugs Fund from BMS
   - analysis according to PD-L1 groups
   - appendix with 2-year stopping rule
   - response to request for additional information

9. **Critique of BMS additional evidence** provided by Kleijnen Systematic Reviews

10. **Additional questions from NICE to Bristol-Myers Squibb (BMS), and their response**

11. **Position statement from the company,** Bristol-Myers Squibb

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

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4th May 2017

Re: Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy [ID971] – company response to Appraisal Consultation Document (ACD)

Dear Helen,

Bristol-Myers Squibb (BMS) Pharmaceuticals Limited would like to thank NICE for the opportunity to comment on the ACD for nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy [ID971].

We are highly disappointed that the Appraisal Committee has ignored the clinical expert feedback and Evidence Review Group (ERG) base case in coming to this preliminary decision not to recommend nivolumab for this patient group. We hope that the Committee will reconsider the evidence and work with BMS to make nivolumab available for this patient population. These patients have a considerable unmet need for innovative treatments that can offer a meaningful extension to life. We believe that the basis for this decision relies on the adoption of an overly pessimistic set of assumptions for considering the cost-effectiveness of nivolumab, which are not supported by the evidence available. BMS have presented additional survival data and revised utility analysis in an accompanying document to this response (*'Response to ACD: additional evidence'*) to address the Committee's concerns regarding the cost-effectiveness of nivolumab for this indication. The result is a revised base case analysis using appropriate utility values from which a range of plausible incremental cost-effectiveness ratios (ICERs) can be considered.

BMS welcome the opportunity to present our response to this preliminary recommendation from NICE and, based on the results of this revised base case analysis, hope that the Committee will revisit their preliminary decision regarding the cost-effectiveness of nivolumab as a treatment for patients with squamous cell carcinoma of the head and neck after platinum-based chemotherapy.

Yours sincerely,

Sarah Breen

Senior HEOR Manager

Bristol-Myers Squibb Pharmaceuticals Limited – Response to Appraisal Consultation Document for ID971

Contents:

The BMS response to the ACD is presented below. Our major concern with the ACD is that the cost-effectiveness estimates informing the preliminary recommendation are founded on the selection of a piecewise-exponential approach for modelling the survival distribution of patients receiving nivolumab. We accept that data limitations in terms of follow-up from the CheckMate 141 trial for patients with recurrent or metastatic (R/M) SCCHN after platinum-based chemotherapy mean that there is unavoidable uncertainty in the long-term survival estimates with nivolumab in this indication. Nevertheless, we strongly believe that the selection of a piecewise-exponential approach is overly pessimistic in that it does not reflect the available evidence from CheckMate 141 and does not provide a plausible long-term survival pattern for patients treated with nivolumab based on evidence from other indications. This issue is the focus of Part 1 of our response. In Part 2 of our response, a factual accuracy correction for the ACD is proposed.

Furthermore, revised cost-effectiveness estimates have been presented in *'Response to ACD: additional evidence – Appendix 2'* to address some of the concerns of the Committee regarding the uncertainty surrounding utility values and the application of a stopping rule, with appropriate treatment-independent utility values presented in *'Response to ACD: additional evidence – Appendix 1'*. The analyses presented in *Appendix 2* use extrapolation approaches that BMS consider to be more plausible than the piecewise exponential approach currently preferred by the Committee, based on the evidence available (as discussed in Part 1).

In considering these revised ICERs, BMS hope that the Committee will revisit their preliminary decision regarding the cost-effectiveness of nivolumab for patients with R/M SCCHN after platinum-based chemotherapy.

Part 1: Approach to modelling long-term survival on nivolumab

In the ACD, the Committee concluded that a piecewise approach using an exponential curve was "more plausible" for extrapolating overall survival on nivolumab, based on uncertainty in longer-term predicted survival estimates. BMS contest that the piecewise-exponential

approach and resultant decision-making ICERs should not be considered to be the *most plausible* as they are associated with the following serious limitations:

1. The approach indicates substantially lower 2-year survival than was observed in the observed Checkmate-141 trial data (see Table 1)

2. Logical inconsistencies exist with this approach; namely, that patients who have died are still modelled to receive treatment with nivolumab

3. The approach contradicts the long-term survival evidence from other trials which provide clear evidence of a decreasing hazard with nivolumab from around three years onwards

These limitations are discussed in more detail below and build upon those presented as part of the original additional evidence submission in which we reasoned that the exponential piecewise approach was less appropriate for the modelling of overall survival with nivolumab.

1. Use of a piecewise exponential extrapolation less accurately reflects empirical data on survival up to a 2-year time point available from the CheckMate 141 study, compared to alternative approaches

In order to assess the validity of using the piecewise-exponential approach, estimates of overall survival over the first two years of the model are presented in Table 1, alongside survival rates from the nivolumab arm of CheckMate 141. By 24 months, the piecewise-exponential approach systematically (i.e. regardless of cut-off point) underestimates survival rates compared to CheckMate 141. This underestimate can only reasonably be expected to become further accentuated across later time points (3, 4, 5 years and so on). The piecewise-lognormal approach and the fully parametric lognormal approach provide a much better fit to the observed survival estimates from CheckMate 141 at 24 months and are explored further in *'Response to ACD: additional evidence – Appendix 2'* as part of the revised base case analysis.

As detailed in previous evidence submissions, these alternative approaches also provide long-term survival estimates that do not overestimate overall survival for nivolumab relative to observed survival in squamous NSCLC trials, which have longer follow-up than CheckMate 141. In addition, the use of the lognormal curve has been accepted by the ERG on a two occasions of review and validated by clinical experts as part of the original Company Evidence Submission. The survival trend predicted by the lognormal curve is consistent with the possibility that a plateau-like shape may be observed in patients with R/M SCCHN, as has been observed in other indications with trials of longer follow-up (see point 3 of Part 1 below). Feedback from a clinical expert consulted by NICE as part of this appraisal and presented in the Committee Papers (page 710) supports an expectation for a plateau to emerge with further follow-up of R/M SCCHN patients receiving nivolumab:

"*Any estimate of likely survival should include a long-term, durable plateau around 7–15%*."

Table 1: Comparison of modelled survival estimates with 2-year survival data from CheckMate 141

Survival curve	Cut-off point (weeks)	Proportion alive, %			Magnitude of difference to CheckMate 141 value at 24 months (as percentage of CheckMate 141 value)
		12 months	18 months	24 months	
Piecewise					
Exponential (Committee preferred)	20	34.4	20.4	13.0	-17.72%
	28	34.7	19.8	12.3	-22.15%
	36	33.9	20.4	13.3	-15.82%
	48	33.1	20.9	14.1	-10.76%
Lognormal	20	32.7	21.9	16.7	+5.70%
	36	31.9	21.3	16.6	+5.06%
	48	34.1	20.3	14.1	-10.76%
Fully parametric					
Lognormal (BMS and ERG preferred)	-	32.9	22.0	16.5	+4.43%
CheckMate 141	-	34.0	21.5	15.8	-

Source: CheckMate 141 CSR Addendum (17th November 2016) –Table 6.1.1.[1]

2. Use of a piecewise exponential approach results in logical inconsistencies

As noted in the original additional evidence submission, the use of the piecewise exponential approach produces logical inconsistencies in which overall survival with nivolumab falls below both progression-free survival (PFS) and time to discontinuation (TTD) during the model time horizon when using the preferred curve selections for PFS and TTD. These logical inconsistencies exist for all cut-off points that have been explored (20, 28, 36 and 48 weeks) and presented in the ACD as the committee-preferred, most plausible ICERs. The consequence of these logical inconsistencies is that patients who have died in the model are still modelled to receive treatment and accrue associated costs, which is clearly not appropriate.

In contrast, the alternative extrapolation approaches used in the revised base case (fully parametric lognormal and piecewise lognormal) are not associated with such logical inconsistencies.

3. An exponential distribution assumes constant hazard of death; this is empirically contradictory to log cumulative hazard and Kaplan-Meier plots that find evidence of decreasing hazards of death with nivolumab in other indications

In the absence of longer-term data for patients with SCCHN, survival data from nivolumab-treated patients with squamous non-small cell lung cancer (NSCLC) have been presented previously as part of this appraisal in order to validate estimates of long-term survival for nivolumab-treated patients with SCCHN. Evidence from trials in patients with NSCLC suggests that the hazard of death with nivolumab is not linear (see cumulative hazards plot from CheckMate 003 – squamous and non-squamous NSCLC; Figure 1), [redacted] (see Kaplan-Meier plots; Figure 2 and Figure 3, respectively). [redacted]

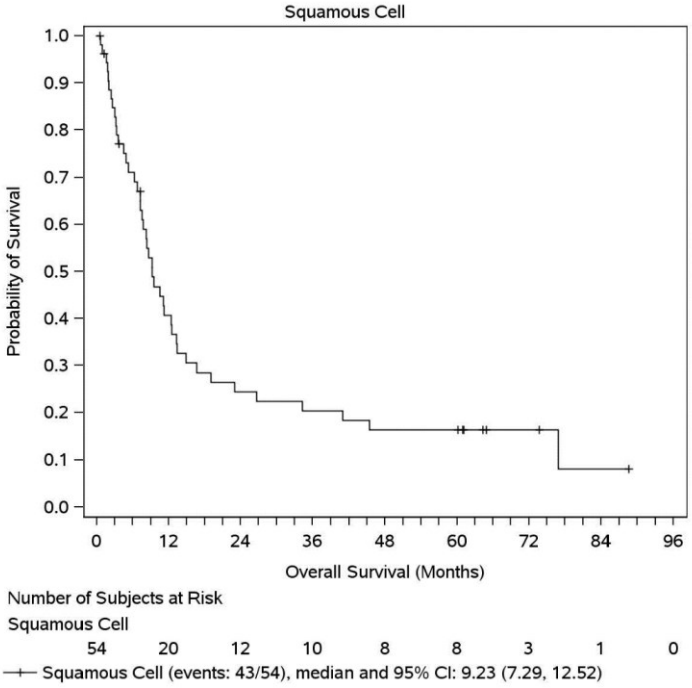
[redacted]

Figure 1: Cumulative hazards plot from CheckMate 003 (NSCLC)


[redacted]

Abbreviations: NSCLC: non-small cell lung cancer.

Figure 2: Kaplan-Meier plot of 5-year overall survival data from CheckMate 003 (squamous NSCLC) – *as presented in additional Company Evidence Submission*



Symbols represent censored observations.
Survival is based on the 11NOV2016 data cutoff and 15NOV2016 data base lock.

Abbreviations: CI: confidence intervals; NSCLC: non-small cell lung cancer.
Source: 5-year survival data from CheckMate 003 have been presented by Brahmer *et al.* (2017)[2]

Figure 3: Kaplan-Meier plot of 3-year overall survival data from CheckMate 017 (squamous NSCLC)

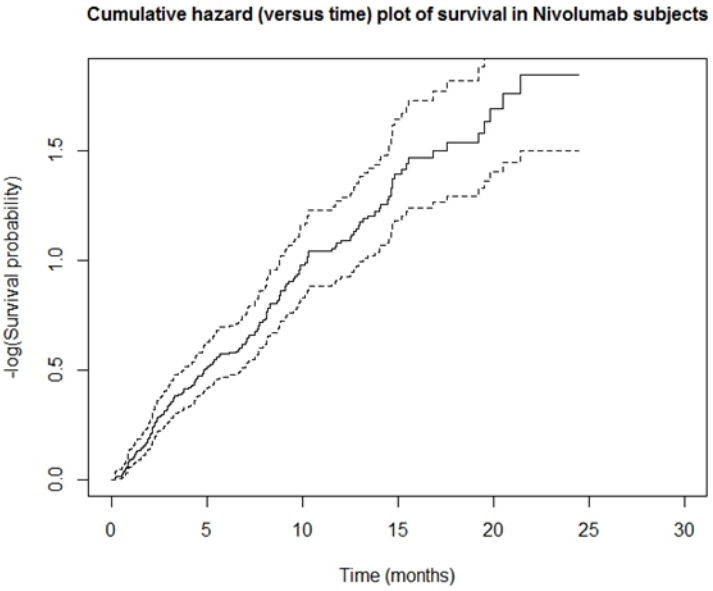
Abbreviations: CI: confidence intervals; NSCLC: non-small cell lung cancer.

The 2-year survival data from CheckMate 141 (R/M SCCHN patients after platinum-based chemotherapy) does not rule out the possibility that a non-linear (i.e. decreasing) hazard of death could exist with longer follow-up. The cumulative hazards plot from CheckMate 141 closely follows that of CheckMate 003 during the first 20 months (see Figure 1 above for CheckMate 003 and Figure 4 below for CheckMate 141), [redacted]. Similarly, the Kaplan-Meier plot for CheckMate 141 appears to be similar in shape to those from CheckMate 003 and CheckMate 017 up to the point at which follow-up is available for CheckMate 141 (see Figure 2 and Figure 3 above for CheckMate 003 and CheckMate 017, and Figure 5 below for CheckMate 141). Survival rates based on Kaplan-Meier estimates also suggest a similar (albeit slightly reduced) survival trend for R/M SCCHN patients in CheckMate 141 compared to squamous NSCLC from CheckMate 003 and CheckMate 017 (see Table 2).

A similar survival trend to that observed in CheckMate 003 and CheckMate 017, as described above, is plausible for patients with R/M SCCHN given the similarities between these conditions in terms of tumour histology, patient characteristics (e.g. age, smoking status – see Appendix 5 of the original Company Evidence Submission for a comparison of the baseline characteristics between CheckMate 141, 003 and 017) and prognosis (patients in the comparator arm of CheckMate 017, docetaxel 75 mg/m^2 Q3W, had a median overall survival of [redacted]). Furthermore, given the durable survival benefits seen in all other cancer indications for which nivolumab has been studied (melanoma and renal cell

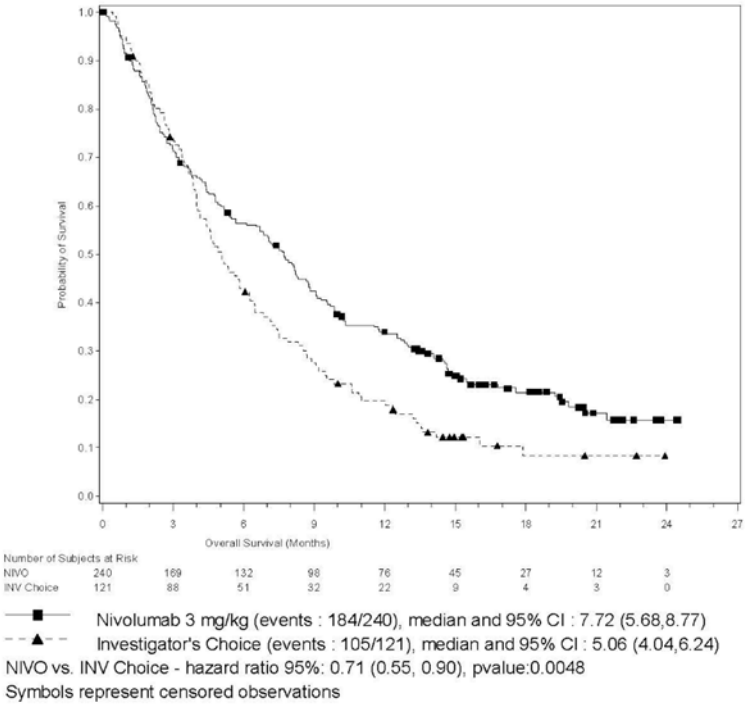
carcinoma), it may be expected that similar long-term survival benefits will also be observed for patients with R/M SCCHN, as noted by a clinical expert consulted by NICE (page 710 of Committee Papers).

Figure 4: Cumulative hazards plot from CheckMate 141 (R/M SCCHN)



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

Figure 5: Kaplan-Meier plot of 2-year overall survival data from CheckMate 141 (R/M SCCHN) – *as presented in additional Company Evidence Submission*



Abbreviations: CI: confidence interval; INV Choice: investigator's choice; NIVO: nivolumab; R/M SCCHN: recurrent or metastatic squamous cell carcinoma of the head and neck.
Source: CheckMate 141 CSR Addendum (17th November 2016) – Figure 6.1-1.[1]

Table 2: Survival rates from CheckMate 141, CheckMate 017 and CheckMate 003

Proportion alive, %	CheckMate 141		CheckMate 017		CheckMate 003 (squamous only)
	Nivolumab	IC	Nivolumab	Docetaxel	Nivolumab
12 months	34.0	19.7	42.2	24.1	41
18 months	21.5	8.3	28.1	12.4	-
24 months	15.8	NA	23.0	8.0	24

Abbreviations: IC: investigator's choice; NA: not achieved.
Sources: CheckMate 141 CSR Addendum (17th November 2016) –Table 6.1.1.,[1] Borghaei *et al.* (2016) [CheckMate 017],[3] Brahmer *et al.* (2017) [CheckMate 003][2]

Based on the latest evidence available from each of these trials, BMS do not believe that an assumption of a constant hazard of death is the most appropriate and therefore urge the Committee to reconsider whether the piecewise-exponential approach is the *most plausible* approach for extrapolating overall survival with nivolumab. BMS acknowledge that, in the face of uncertainty around long-term survival, the use of the piecewise-exponential approach provides a (highly) conservative estimate of survival. However, this does not necessarily mean that the piecewise-exponential approach is the most appropriate, as noted by the DSU in ID811:

"[redacted]."

The appropriateness of the piecewise-exponential approach with regards to clinical plausibility has been explored above in point 1 of Part 1.

Summary of considerations for approach to modelling survival

BMS acknowledge that there is insufficient maturity of data from the CheckMate 141 trial to determine with complete certainty the true estimate of long-term survival with nivolumab for patients with R/M SCCHN after platinum-based chemotherapy. However, by selecting the piecewise exponential approach, we do not believe that the choice made by the Committee represents a choice that adequately reflects the uncertainty as to whether the pattern of long-term survival with nivolumab in R/M SCCHN patients will follow that observed in other indications; rather it is an explicit choice not to account for this uncertainty by assuming that a similar pattern of decreasing hazards will not be observed. We therefore consider this to represent a pessimistic and overly conservative selection, rather than one that considers the uncertainty and represents what is most plausible based on the evidence that is available from CheckMate 141 and the other nivolumab trials. A revised base case using the alternative approaches to modelling overall survival (piecewise-lognormal approach or fully parametric lognormal approach), that allow for the possibility of decreasing hazards, is therefore presented in *'Response to ACD: additional evidence – Appendix 2'* for the Committee's consideration.

Part 2: Factual inaccuracy correction

Section 4.16 – page 14 of the ACD

Having reviewed the ACD, BMS have concerns over the 'treatment-independent' utility scenario presented in the ACD (see Section 4.16 of the ACD):

"*In a scenario analysis, the ERG used treatment-independent utilities to account for this uncertainty and for the missing data. This increased the company's ICER range for the scenario without a stopping rule from between £44,000 and £47,000 per quality-adjusted life year (QALY) gained to between £62,000 and £67,000 per QALY gained.*"

The ICERs reported from this scenario (£62,000 and £67,000 per QALY gained; with PAS for nivolumab) in fact relate to a scenario conducted by the ERG in which a disutility of 0.149 (the difference in post-progression utility between treatment arms) was applied to patients in the nivolumab arm that discontinued treatment (see Table 5 of the addendum to the ERG review of the additional Company Evidence Submission). This does not relate to a scenario using treatment-independent utilities and so is somewhat factually inaccurate. BMS believe that it would more accurate to present ICERs using the ERG's estimates of treatment-independent utility values ([redacted] for progression free and [redacted] for progressed disease), as detailed in Table 4 of the addendum to the ERG review of the additional Company Evidence Submission.

The cost-effectiveness results using the company-preferred assumptions, as per the ACD (i.e. fully parametric lognormal approach to modelling overall survival and no stopping rule), with the ERG's estimates of treatment-independent utility values are presented in Table 3.

Table 3: Cost-effectiveness results using the ERG's estimates of treatment-independent utility values (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.39	[redacted]	0.52	[redacted]	£59,003
Paclitaxel	11,881	0.67	0.39	[redacted]	0.52	[redacted]	£54,748
Methotrexate	11,536	0.67	0.39	[redacted]	0.52	[redacted]	£55,798

Abbreviations: ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; LY(G): life years (gained); PAS: Patient Access Scheme; QALY: quality-adjusted life year.

References

1. Bristol-Myers Squibb. CheckMate 141: Addendum 01 to the Final Clinical Study Report for Study CA209141 (17th November 2016).
2. Brahmer J, Horn L, Jackman DM, et al. CT077 - Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer (NSCLC): Clinical characteristics of long-term survivors. Presented at the American Association for Cancer Research annual meeting - Washington DC 2017. Abstract number CT077. 2017.
3. Borghaei H, Brahmer J, Horn L, et al. Nivolumab (nivo) vs docetaxel (doc) in patients (pts) with advanced NSCLC: CheckMate 017/057 2-y update and exploratory cytokine profile analyses. J Clin Oncol 2016;34.

The Royal College of Pathologists
Pathology: the science behind the cure

Royal College of Pathologists Response: Appraisal consultation document Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

The Royal College of Pathologists consider that the NICE Committee has considered and made a reasonable interpretation of the evidence presented.

These recommendations are sound and suitable for the NHS and have considered relevant aspects of this mode of treatment for head and neck cancer.

Response from Dr. Anthony Kong

I am disappointed with the conclusions from the appraisal committee and Nivolumab was thought not to be cost-effective for NHS use since ICER was likely to be > £50000 per QALY gained. However, there is a discrepancy in the calculated ICER between the ERG and the company, with the company's calculation being less than £50000 per QALY. I would like to raise the following points, which partly account for the differences:

1) I do not agree with ERG that exponential curve was more plausible since there is a plateau in the survival curve seen in a small minority of patients treated with nivolumab because of long-term survival, beyond what is seen with palliative chemotherapy. Although we do not have the definitive long-term data from HNSCC yet, we could infer the long-term survival data from patients with lung cancers, which are similar to HNSCC patients.

2) I do not agree that no stopping rule is used as it is inevitable that some responding patients will stop treatment after a while due to a variety of reason, for example physicians or patients' choices (maybe due to toxicities) and also increasingly, immunotherapy is now stopped after a period of time since some patients may continue to derive benefit. This is now done in a few HNSCC trials. Therefore, I would think that 25% stopping rule is reasonable.

3) I disagree with ERG from using treatment-independent utilities for the ICER calculation. For immunotherapy, there is a small group of responding patients, who have an excellent quality of life and minimal toxicities and have a long-term survival, even after the treatment is stopped. Some of these responding patients may subsequently progress according to RECIST criteria. However, even in this 'disease-progressed' state, some may continue derive benefit from previous immunotherapy and may remain in good health for a period of time with a longer-term survival, which is not seen with palliative chemotherapy. This is not captured in the ERG's treatment–independent calculation, which greatly increased the ICER and beyond the threshold value of £50000 per QALY.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Clinical Oncologist
Organisation	[redacted]
Location	England
Conflict	Yes Disclosure of potential conflict of interest: I have received payment from BMS for attending advisory boards and speaking in their promotional meetings. I have also been supported by BMS for my academic conference attendances.
Notes	
Comments on individual sections of the ACD:	
General comments	The committee disagreed with the assumption that the treatment effect of Nivolumab can last for 20 years, or even 5-10 as revised by the company, and questioned whether the survival benefit would stay constant up to 5 years irrespective of treatment duration. I disagreed with the committee's doubt. From our experience with the use of PD-1 inhibitor (Pembrolizumab and Nivolumab) in other sites such as lung and melanoma, we do see a group of patients who can derive DURABLE response measured in terms of years after they have stopped their treatment. This is the uniqueness of immunotherapy compared to conventional chemotherapy. The percentage varies for different tumour sites; for melanoma it is about 40%, for lung it is about 20% but this is a genuine phenomenon. Looking at the result of CheckMate 141 as presented in Autumn 2016, the object RECIST response rate is about 13%, translating to an 8.2% PFS in the September 2016 data-lock. I think it is highly credible that a significant proportion of these patients will end up having their disease under control for many years, and this should be taken into account in calculating the ICER and can persist for 5-10 years if not longer. This leads on to point 4.14 - 2 years is the standard duration that patients with lung and melanoma patients receive their treatment for hence I think the 2 year stopping rule proposed by the company is perfectly reasonable and in line with routine clinical use of this class of drug in melanoma and lung cancer patients. This brings me back to point 4.11 in which the committee did not consider it plausible that the risk of death would almost become similar to that of the general population towards the end of the model's 20 year time horizon. In view of the durable response achievable with immunotherapy I think this is highly plausible.

Name	NCRI Head & Neck CSG
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on individual sections of the ACD:	
General comment	Dear Committee members We, on behalf of the NCRI Head & Neck CSG, have read the outcome from the recent appraisal review of 'Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy' with both interest and ultimately disappointment. We understand the provisional recommendations are not to recommend nivolumab within this setting and would like to make a few comments on the appraisal and conclusions made, outlined below: 1. We agree that all the clinical need, patient population and relevant data, essentially the data from the CheckMate 141 study, have been reviewed. 2. We do not have concerns about the comparator therapies and the relevance of the trial results to the UK population: Methotrexate is considered an acceptable standard chemotherapy within this setting with no evidence to demonstrate it is inferior to other agents such as a taxane. Whilst it is not used as frequently within the Uk, it is particularly used in countries where taxane based therapy is used more routinely as induction chemotherapy or as concurrent chemo-radiotherapy, or in combination with platinum as first line therapy for relapsed / metastatic disease. Cetuximab is a FDA-approved therapy used in the US and whilst not approved, or used, within the UK in this setting, it has single agent activity and the 12% of patients treated with cetuximab within this study should not significantly question the relevance of this study for the UK population. 3. We do not feel that the use of exponential survival curves are the most relevant for nivolumab in this population. The Overall Survival Data will mature over time but the data so far are very compelling. As seen within this study the survival curves do not separate immediately and therefore whilst median overall survival improvements are important, improvements in survival at later time points, such as the doubling of OS at 12 months demonstrated in this study, show the improved duration of response within the responding population that drives the real benefit of nivolumab within recurrent Head & Neck Cancer. This is a consistent effect seen with this class of drugs across multiple tumour types. Whilst the longer term survival impact of nivolumab in H&N SqCC within

	this study is projected, due to the maturity of the data presented, the experience with nivolumab within other studies where data are more mature, including in NSCLC which occurs in a similar patient population to H&N SqCC, show a plateau'd benefit with a proportion of responding patients gaining durable benefit. Therefore we feel that the insistence on using an exponential curve is NOT appropriate in this setting and likely to underestimate the benefit of nivolumab. 4. We disagree with the concept that a 'no stopping rule' applies. The use of PD-1 inhibitors in both studies and clinical practice including a defined length of therapy is well established and whilst the optimal duration of therapy remains to be determined the vast majority of patients, even those responding to therapy, will stop treatment at some point. This is exampled by the NICE technology appraisal TA428 in lung cancer. We feel that a 25% stopping rule seemed reasonable and appropriate for this relapsed / metastatic H&N SqCC population. 5. We agree that the preplanned sub-group analysis of PD-L1 status is suggestive that the benefit is more clearly seen in patients whose tumours express PD-L1 >1% but emphasise that benefit was seen across the whole trial population. 6. We felt that the use of treatment-independent utilities for the ICER is not reflective of the difference between the treatments evaluated. First, the tendency towards improvement in QoL indicators in the nivolumab arm (with reduction in these indicators within the chemotherapy arm) is entirely in keeping with clinical experience in that nivolumab is very well tolerated in contrast to chemotherapy in this setting. In addition there is increasing evidence across multiple tumour types that ongoing benefit is seen beyond stopping immunotherapy, with a proportion of patients responding to immunotherapy having a very durable response with excellent quality of life. This benefit may be maintained beyond progression, associated with a longer period of survival with good quality of life even after stopping medication and with progressing disease. Many thanks NCRI H&N CSG

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Bristol-Myers Squibb	In the ACD, the Committee concluded that a piecewise approach using an exponential curve was “more plausible” for extrapolating overall survival on nivolumab, based on uncertainty in longer-term predicted survival estimates. BMS contest that the piecewise-exponential approach and resultant decision-making ICERs should not be considered to be the most plausible as they are associated with the following serious limitations: 1. The approach indicates substantially lower 2-year survival than was observed in the observed Checkmate-141 trial data (see Table 1) 2. Logical inconsistencies exist with this approach; namely, that patients who have died are still modelled to receive treatment with nivolumab 3. The approach contradicts the long-term survival evidence from other trials which provide clear evidence of a decreasing hazard with nivolumab from around three years onwards These limitations are discussed in more detail below and build upon those presented as part of the original additional evidence submission in which we reasoned that the exponential piecewise approach was less appropriate for the modelling of overall survival with nivolumab.	Thank you for your comments. Given the inconsistencies with the piecewise exponential model, the committee accepted the company’s piecewise log-normal model (section 3.12 of the FAD).

2	Company	Bristol-Myers Squibb	**Use of a piecewise exponential extrapolation less accurately reflects empirical data on survival up to a 2-year time point available from the CheckMate 141 study, compared to alternative approaches** In order to assess the validity of using the piecewise-exponential approach, estimates of overall survival over the first two years of the model are presented in Table 1, alongside survival rates from the nivolumab arm of CheckMate 141. By 24 months, the piecewise-exponential approach systematically (i.e. regardless of cut-off point) underestimates survival rates compared to CheckMate 141. This underestimate can only reasonably be expected to become further accentuated across later time points (3, 4, 5 years and so on). The piecewise-lognormal approach and the fully parametric lognormal approach provide a much better fit to the observed survival estimates from CheckMate 141 at 24 months and are explored further in 'Response to ACD: additional evidence – Appendix 2' as part of the revised base case analysis. As detailed in previous evidence submissions, these alternative approaches also provide long-term survival estimates that do not overestimate overall survival for nivolumab relative to observed survival in squamous NSCLC trials, which have longer follow-up than CheckMate 141. In addition, the use of the lognormal curve has been accepted by the ERG on a two occasions of review and validated by clinical experts as part of the original Company Evidence Submission. The survival trend predicted by the lognormal curve is consistent with the possibility that a plateau-like shape may be observed in patients with R/M SCCHN, as has been observed in other indications with trials of longer follow-up (see point 3 of Part 1 below). Feedback from a clinical expert consulted by NICE as part of this appraisal and presented in the Committee Papers (page 710) supports an expectation for a plateau to emerge with further follow-up of R/M SCCHN patients receiving nivolumab: "Any estimate of likely survival should include a long-term, durable plateau around 7–15%." Table 1: Comparison of modelled survival estimates with 2-year survival data from CheckMate 141 *[table provided but not reproduced here]*	Thank you for your comments. Given the inconsistencies with the piecewise exponential model, the committee accepted the company's piecewise log-normal model (section 3.12 of the FAD).

3	Company	Bristol-Myers Squibb	**Use of a piecewise exponential approach results in logical inconsistencies** As noted in the original additional evidence submission, the use of the piecewise exponential approach produces logical inconsistencies in which overall survival with nivolumab falls below both progression-free survival (PFS) and time to discontinuation (TTD) during the model time horizon when using the preferred curve selections for PFS and TTD. These logical inconsistencies exist for all cut-off points that have been explored (20, 28, 36 and 48 weeks) and presented in the ACD as the committee-preferred, most plausible ICERs. The consequence of these logical inconsistencies is that patients who have died in the model are still modelled to receive treatment and accrue associated costs, which is clearly not appropriate. In contrast, the alternative extrapolation approaches used in the revised base case (fully parametric lognormal and piecewise lognormal) are not associated with such logical inconsistencies.	Thank you for your comments. Given the inconsistencies with the piecewise exponential model, the committee accepted the company's piecewise log-normal model (section 3.12 of the FAD).

4	Company	Bristol-Myers Squibb	**An exponential distribution assumes constant hazard of death; this is empirically contradictory to log cumulative hazard and Kaplan-Meier plots that find evidence of decreasing hazards of death with nivolumab in other indications** In the absence of longer-term data for patients with SCCHN, survival data from nivolumab-treated patients with squamous non-small cell lung cancer (NSCLC) have been presented previously as part of this appraisal in order to validate estimates of long-term survival for nivolumab-treated patients with SCCHN. Evidence from trials in patients with NSCLC suggests that the hazard of death with nivolumab is not linear (see cumulative hazards plot from CheckMate 003 – squamous and non-squamous NSCLC; **Error! Reference source not found.**), [redacted] (see Kaplan-Meier plots; **Error! Reference source not found.** and **Error! Reference source not found.**, respectively). [redacted] Figure 1: Cumulative hazards plot from CheckMate 003 (NSCLC) *[Figure provided but not reproduced here]* Figure 2: Kaplan-Meier plot of 5-year overall survival data from CheckMate 003 (squamous NSCLC) – as presented in additional Company Evidence Submission *[Figure provided but not reproduced here]* Figure 3: Kaplan-Meier plot of 3-year overall survival data from CheckMate 017 (squamous NSCLC) *[Figure provided but not reproduced here]*	Thank you for your comments. Given the inconsistencies with the piecewise exponential model, the committee accepted the company's piecewise log-normal model (section 3.12 of the FAD).

			The 2-year survival data from CheckMate 141 (R/M SCCHN patients after platinum-based chemotherapy) does not rule out the possibility that a non-linear (i.e. decreasing) hazard of death could exist with longer follow-up. The cumulative hazards plot from CheckMate 141 closely follows that of CheckMate 003 during the first 20 months (see **Error! Reference source not found.** above for CheckMate 003 and **Error! Reference source not found.** below for CheckMate 141), [redacted]. Similarly, the Kaplan-Meier plot for CheckMate 141 appears to be similar in shape to those from CheckMate 003 and CheckMate 017 up to the point at which follow-up is available for CheckMate 141 (see **Error! Reference source not found.** and **Error! Reference source not found.** above for CheckMate 003 and CheckMate 017, and **Error! Reference source not found.** below for CheckMate 141). Survival rates based on Kaplan-Meier estimates also suggest a similar (albeit slightly reduced) survival trend for R/M SCCHN patients in CheckMate 141 compared to squamous NSCLC from CheckMate 003 and CheckMate 017 (see **Error! Reference source not found.**). A similar survival trend to that observed in CheckMate 003 and CheckMate 017, as described above, is plausible for patients with R/M SCCHN given the similarities between these conditions in terms of tumour histology, patient characteristics (e.g. age, smoking status – see Appendix 5 of the original Company Evidence Submission for a comparison of the baseline characteristics between CheckMate 141, 003 and 017) and prognosis (patients in the comparator arm of CheckMate 017, docetaxel 75 mg/m^2 Q3W, had a median overall survival of [redacted]). Furthermore, given the durable survival benefits seen in all other cancer indications for which nivolumab has been studied (melanoma and renal cell carcinoma), it may be expected that similar long-term survival benefits will also be observed for patients with R/M SCCHN, as noted by a clinical expert consulted by NICE (page 710 of Committee Papers). Figure 4: Cumulative hazards plot from CheckMate 141 (R/M SCCHN) *[Figure provided but not reproduced here]* Figure 5: Kaplan-Meier plot of 2-year overall survival data from CheckMate 141 (R/M SCCHN) – as presented in additional Company Evidence Submission *[Figure provided but not reproduced here]* Table 2: Survival rates from CheckMate 141, CheckMate 017 and CheckMate 003 *[Table provided but not reproduced here]*	Thank you for your comments. Given the inconsistencies with the piecewise exponential model, the committee accepted the company's piecewise log-normal model (section 3.12 of the FAD).

			Based on the latest evidence available from each of these trials, BMS do not believe that an assumption of a constant hazard of death is the most appropriate and therefore urge the Committee to reconsider whether the piecewise-exponential approach is the most plausible approach for extrapolating overall survival with nivolumab. BMS acknowledge that, in the face of uncertainty around long-term survival, the use of the piecewise-exponential approach provides a (highly) conservative estimate of survival. However, this does not necessarily mean that the piecewise-exponential approach is the most appropriate, as noted by the DSU in ID811: "[redacted]." The appropriateness of the piecewise-exponential approach with regards to clinical plausibility has been explored above in point 1 of Part 1.	
5	Company	Bristol-Myers Squibb	**Summary of considerations for approach to modelling survival** BMS acknowledge that there is insufficient maturity of data from the CheckMate 141 trial to determine with complete certainty the true estimate of long-term survival with nivolumab for patients with R/M SCCHN after platinum-based chemotherapy. However, by selecting the piecewise exponential approach, we do not believe that the choice made by the Committee represents a choice that adequately reflects the uncertainty as to whether the pattern of long-term survival with nivolumab in R/M SCCHN patients will follow that observed in other indications; rather it is an explicit choice not to account for this uncertainty by assuming that a similar pattern of decreasing hazards will not be observed. We therefore consider this to represent a pessimistic and overly conservative selection, rather than one that considers the uncertainty and represents what is most plausible based on the evidence that is available from CheckMate 141 and the other nivolumab trials. A revised base case using the alternative approaches to modelling overall survival (piecewise-lognormal approach or fully parametric lognormal approach), that allow for the possibility of decreasing hazards, is therefore presented in 'Response to ACD: additional evidence – Appendix 2' for the Committee's consideration.	Thank you for your comments. Given the inconsistencies with the piecewise exponential model, the committee accepted the company's piecewise log-normal model (section 3.12 of the FAD).

6	Company	Bristol-Myers Squibb	**Section 4.16 – page 14 of the ACD** Having reviewed the ACD, BMS have concerns over the 'treatment-independent' utility scenario presented in the ACD (see Section 4.16 of the ACD): "*In a scenario analysis, the ERG used treatment-independent utilities to account for this uncertainty and for the missing data. This increased the company's ICER range for the scenario without a stopping rule from between £44,000 and £47,000 per quality-adjusted life year (QALY) gained to between £62,000 and £67,000 per QALY gained.*" The ICERs reported from this scenario (£62,000 and £67,000 per QALY gained; with PAS for nivolumab) in fact relate to a scenario conducted by the ERG in which a disutility of [redacted] (the difference in post-progression utility between treatment arms) was applied to patients in the nivolumab arm that discontinued treatment (see Table 5 of the addendum to the ERG review of the additional Company Evidence Submission). This does not relate to a scenario using treatment-independent utilities and so is somewhat factually inaccurate. BMS believe that it would more accurate to present ICERs using the ERG's estimates of treatment-independent utility values ([redacted] for progression free and [redacted] for progressed disease), as detailed in Table 4 of the addendum to the ERG review of the additional Company Evidence Submission. The cost-effectiveness results using the company-preferred assumptions, as per the ACD (i.e. fully parametric lognormal approach to modelling overall survival and no stopping rule), with the ERG's estimates of treatment-independent utility values are presented in Table 1. Table 1: Cost-effectiveness results using the ERG's estimates of treatment-independent utility values (with PAS for nivolumab) *[Table provided but not reproduced here]*	Thank you for your comments. See section 3.18 of the FAD for the committee's conclusion on the most appropriate utility values.
7	Clinical expert		I do not agree with ERG that exponential curve was more plausible since there is a plateau in the survival curve seen in a small minority of patients treated with nivolumab because of long-term survival, beyond what is seen with palliative chemotherapy. Although we do not have the definitive long-term data from HNSCC yet, we could infer the long-term survival data from patients with lung cancers, which are similar to HNSCC patients.	Thank you for your comments. Given the inconsistencies with the piecewise exponential model, the committee accepted the company's piecewise log-normal model (section 3.12 of the FAD).

8	Clinical expert		I do not agree that no stopping rule is used as it is inevitable that some responding patients will stop treatment after a while due to a variety of reason, for example physicians or patients' choices (maybe due to toxicities) and also increasingly, immunotherapy is now stopped after a period of time since some patients may continue to derive benefit. This is now done in a few HNSCC trials. Therefore, I would think that 25% stopping rule is reasonable.	Thank you for your comments. The committee considered a stopping rule in the context of including nivolumab in the CDF. See sections 3.16 and 3.25 of the FAD.
9	Clinical expert		I disagree with ERG from using treatment-independent utilities for the ICER calculation. For immunotherapy, there is a small group of responding patients, who have an excellent quality of life and minimal toxicities and have a long-term survival, even after the treatment is stopped. Some of these responding patients may subsequently progress according to RECIST criteria. However, even in this 'disease-progressed' state, some may continue derive benefit from previous immunotherapy and may remain in good health for a period of time with a longer-term survival, which is not seen with palliative chemotherapy. This is not captured in the ERG's treatment–independent calculation, which greatly increased the ICER and beyond the threshold value of £50000 per QALY.	Thank you for your comments. See sections 3.17 and 3.18 of the FAD for the committee's conclusion on the most appropriate utility values.
10	Professional organisation	Royal College of Pathologists	The Royal College of Pathologists consider that the NICE Committee has considered and made a reasonable interpretation of the evidence presented. These recommendations are sound and suitable for the NHS and have considered relevant aspects of this mode of treatment for head and neck cancer.	Thank you for your comments. Nivolumab is now recommended for use within the CDF (see section 1 of the FAD).

11	NHS professional		The committee disagreed with the assumption that the treatment effect of Nivolumab can last for 20 years, or even 5-10 as revised by the company, and questioned whether the survival benefit would stay constant up to 5 years irrespective of treatment duration. I disagreed with the committee's doubt. From our experience with the use of PD-1 inhibitor (Pembrolizumab and Nivolumab) in other sites such as lung and melanoma, we do see a group of patients who can derive DURABLE response measured in terms of years after they have stopped their treatment. This is the uniqueness of immunotherapy compared to conventional chemotherapy. The percentage varies for different tumour sites; for melanoma it is about 40%, for lung it is about 20% but this is a genuine phenomenon. Looking at the result of CheckMate 141 as presented in Autumn 2016, the object RECIST response rate is about 13%, translating to an 8.2% PFS in the September 2016 data-lock. I think it is highly credible that a significant proportion of these patients will end up having their disease under control for many years, and this should be taken into account in calculating the ICER and can persist for 5-10 years if not longer. This leads on to point 4.14 - 2 years is the standard duration that patients with lung and melanoma patients receive their treatment for hence I think the 2 year stopping rule proposed by the company is perfectly reasonable and in line with routine clinical use of this class of drug in melanoma and lung cancer patients. This brings me back to point 4.11 in which the committee did not consider it plausible that the risk of death would almost become similar to that of the general population towards the end of the model's 20 year time horizon. In view of the durable response achievable with immunotherapy I think this is highly plausible.	Thank you for your comments. Based on the evidence presented, the committee concluded that the company's scenario of a continued survival benefit lasting up to 5 years was plausible, but assuming that the benefit would stay constant after treatment stops is uncertain (section 3.15 of the FAD).
12	Research group	NCRI Head & Neck CSG	We agree that all the clinical need, patient population and relevant data, essentially the data from the CheckMate 141 study, have been reviewed.	Thank you for your comments.
13	Research group	NCRI Head & Neck CSG	We do not have concerns about the comparator therapies and the relevance of the trial results to the UK population: Methotrexate is considered an acceptable standard chemotherapy within this setting with no evidence to demonstrate it is inferior to other agents such as a taxane. Whilst it is not used as frequently within the Uk, it is particularly used in countries where taxane based therapy is used more routinely as induction chemotherapy or as concurrent chemo-radiotherapy, or in combination with platinum as first line therapy for relapsed / metastatic disease. Cetuximab is a FDA-approved therapy used in the US and whilst not approved, or used, within the UK in this setting, it has single agent activity and the 12% of patients treated with cetuximab within this study should not significantly question the relevance of this study for the UK population.	Thank you for your comments. No change relating to comparators were made to the FAD.

14	Research group	NCRI Head & Neck CSG	We do not feel that the use of exponential survival curves are the most relevant for nivolumab in this population. The Overall Survival Data will mature over time but the data so far are very compelling. As seen within this study the survival curves do not separate immediately and therefore whilst median overall survival improvements are important, improvements in survival at later time points, such as the doubling of OS at 12 months demonstrated in this study, show the improved duration of response within the responding population that drives the real benefit of nivolumab within recurrent Head & Neck Cancer. This is a consistent effect seen with this class of drugs across multiple tumour types. Whilst the longer term survival impact of nivolumab in H&N SqCC within this study is projected, due to the maturity of the data presented, the experience with nivolumab within other studies where data are more mature, including in NSCLC which occurs in a similar patient population to H&N SqCC, show a plateau'd benefit with a proportion of responding patients gaining durable benefit. Therefore we feel that the insistence on using an exponential curve is NOT appropriate in this setting and likely to underestimate the benefit of nivolumab.	Thank you for your comments. Given the inconsistencies with the piecewise exponential model, the committee accepted the company's piecewise log-normal model (section 3.12 of the FAD).
15	Research group	NCRI Head & Neck CSG	We disagree with the concept that a 'no stopping rule' applies. The use of PD-1 inhibitors in both studies and clinical practice including a defined length of therapy is well established and whilst the optimal duration of therapy remains to be determined the vast majority of patients, even those responding to therapy, will stop treatment at some point. This is exampled by the NICE technology appraisal TA428 in lung cancer. We feel that a 25% stopping rule seemed reasonable and appropriate for this relapsed / metastatic H&N SqCC population	Thank you for your comments. The committee considered a stopping rule in the context of including nivolumab in the CDF. See sections 3.16 and 3.25 of the FAD.
16	Research group	NCRI Head & Neck CSG	We agree that the preplanned sub-group analysis of PD-L1 status is suggestive that the benefit is more clearly seen in patients whose tumours express PD-L1 >1% but emphasise that benefit was seen across the whole trial population.	Thank you for your comments.
17	Research group	NCRI Head & Neck CSG	We felt that the use of treatment-independent utilities for the ICER is not reflective of the difference between the treatments evaluated. First, the tendency towards improvement in QoL indicators in the nivolumab arm (with reduction in these indicators within the chemotherapy arm) is entirely in keeping with clinical experience in that nivolumab is very well tolerated in contrast to chemotherapy in this setting. In addition there is increasing evidence across multiple tumour types that ongoing benefit is seen beyond stopping immunotherapy, with a proportion of patients responding to immunotherapy having a very durable response with excellent quality of life. This benefit may be maintained beyond progression, associated with a longer period of survival with good quality of life even after stopping medication and with progressing disease.	Thank you for your comments. See sections 3.17 and 3.18 of the FAD for the committee's conclusion on the most appropriate utility values.

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Bristol-Myers Squibb Pharmaceuticals Limited – Response to ACD: additional evidence

Appendix 1: Treatment-independent utility values and mixed model output

BMS agree with the Committee and the ERG that the use of treatment-independent utility values represents a conservative approach in that it fails to account for the quality-of-life benefits associated with nivolumab. This benefit, even after treatment has stopped, was demonstrated in the Checkmate 141 trial and in the mixed model analysis, with a statistically significant difference between treatment arms. It was also validated as clinically plausible by the clinical experts consulted as part of this appraisal (see Section 4.16 and 4.17 of the ACD). BMS recognises, however, that the Committee has concerns that the treatment-specific utility values are associated with significant uncertainty and so has addressed these with the provision of revised cost-effectiveness results using treatment-independent utility values (see the *'Response to ACD: additional evidence – Appendix 2'*). These are presented to provide a 'utility pessimistic' estimate of cost-effectiveness where nivolumab offers no quality of life benefit over chemotherapy and are presented alongside ICERs using the treatment-specific utility values used previously ('utility optimistic'), to reflect the Committee's conclusion that the most appropriate utility estimate probably lies between these two values.

To provide a scenario that assumes treatment-independent utilities ('utility pessimistic'), an analysis of the CheckMate 141 EQ-5D data has been conducted which uses a mixed model that only includes progression status (progression free or progressed disease) as a covariate (see Table 1). This analysis is therefore more representative of treatment-independent utilities (as compared to the ERG's previous estimates), as treatment arm is not included as a covariate.

The full output from the mixed-model analysis is provided in Table 2 to allow the ERG to provide a more comprehensive review of the utility analyses than was previously possible. BMS accept and apologise that sufficient information to allow a full critique of these utility values was not provided previously.

Table 1: Treatment-independent utility values (i.e. no quality of life benefit 'utility pessimistic')

Model	Mean utility	
	Progression free / on treatment	Progressed disease / off treatment
With progression status as the only covariate	[redacted]	[redacted]

Table 2: Mixed Models Fixed Effects Parameter Estimates and Fit Statistics

Parameters/Fit Statistics	Model 1: Full Model, Mean (SE), p-value	Model 2: Tx. Arm Dropped, Mean (SE), p-value	Model 3: Prog. Status Dropped, Mean (SE), p-value	Model 4: Tx. Arm Added, Mean (SE), p-value	Model 5[2]: Tx. Status Dropped, Mean (SE), p-value	Model 6: Prog. Status Added, Mean (SE), p-value	Model 7: Prog. Status Only, Mean (SE), p-value
Intercept[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Arm (Investigator's Choice)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression Status (Progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Status (Off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Arm*Progression Status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression Status*Treatment Status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Arm*Treatment Status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Arm*Progression Status*Treatment Status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-2 Res Log Likelihood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC (smaller is better)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AICC (smaller is better)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC (smaller is better)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Generally, mixed models included EQ-5D Utility Index Score as a dependent measure, with the fixed effects of treatment arm, treatment status and progression status. Subject was treated as random effect. A compound symmetry covariance structure was used unless otherwise noted.
[1] Intercept includes Nivolumab treatment arm, on treatment treatment status and non-progression (SD/PR/CR) progression status.
Model 1 included all main effects, all 2 variable and 3 variable interactions. All subsequent models removed main effects and interactions in a stepwise manner.
[2] Model 5 used an autoregressive covariance structure.

Appendix 2: Revised base case and summary of ICERs that have been considered as part of this appraisal to date

1. Revised base case

To address some of the concerns that the Committee have raised in the ACD, a revised base case analysis is presented below for the cost-effectiveness of nivolumab versus each of the relevant comparators (with PAS for nivolumab).

This revised base case includes the Committee's preferred assumptions of:

- No clinical stopping rule
- Treatment-independent utility values (using the mixed model with progression status as the only covariate [i.e. no quality of life benefit: 'utility pessimistic'])

Results are also presented using treatment-specific utility values in order to provide the lower estimate for the cost-effectiveness of nivolumab (i.e. including a quality of life benefit with nivolumab versus chemotherapy: 'utility optimistic'), given all other model assumptions. Based on the Committee's conclusions in the ACD that the utility associated with nivolumab is likely underestimated using treatment-independent values, the most plausible ICER for nivolumab versus each of the comparators is likely to lie between the two values, given the other model settings used.

However, contrary to the Committee's preferences, BMS do not consider it appropriate to use the piecewise-exponential approach to model overall survival with nivolumab, given the evidence presented in Part 1 of the main ACD response. Results have instead been presented here using the company-preferred, fully parametric lognormal approach, which is believed to represent the most plausible estimate of overall survival with nivolumab based on the evidence available from CheckMate 141 and the squamous NSCLC trials. To address the Committee's concern over the suitability of the lognormal curve in terms of fit to the early Kaplan-Meier data (see Section 4.11 of the ACD), results are also presented using a piecewise-lognormal approach that uses Kaplan-Meier data up to a variable cut-off point of 20, 36 or 48 weeks. As per the previous evidence submissions, the same approach to modelling survival has been applied to both the nivolumab and investigator's choice arms.

As shown in Tables 3 to 6, nivolumab (with PAS) is associated ICERs ranging between £40,000 and £69,000 per QALY gained versus each of the relevant comparators, depending on the utility values and piecewise cut-off point chosen. Given that the quality-of-life benefit associated with nivolumab is likely to lie between the two utility scenarios ('pessimistic' and 'optimistic') and that piecewise approaches predict both lower and higher ICERs compared to the fully parametric approach, depending on the cut-off point chosen, BMS hope that these results mitigate some of the uncertainties highlighted by the Committee around the utility values used and the fit of fully parametric survival curves to the early part of the CheckMate 141 Kaplan-Meier data.

Table 3: Cost-effectiveness results from revised base case analysis – fully parametric lognormal approach (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
'Utility pessimistic'							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.41	[redacted]	0.52	[redacted]	£56,940
Paclitaxel	11,881	0.67	0.41	[redacted]	0.52	[redacted]	£52,833
Methotrexate	11,536	0.67	0.41	[redacted]	0.52	[redacted]	£53,847
'Utility optimistic'							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	£47,086
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	£43,690
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	£44,528

Abbreviations: ICER: incremental cost-effectiveness ratio; LY(G): life years (gained); PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Table 4: Cost-effectiveness results from revised base case analysis – piecewise lognormal approach with 20-week cut-off point (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
'Utility pessimistic'							
Nivolumab	[redacted]	1.26	[redacted]				
Docetaxel	10,682	0.77	0.46	[redacted]	0.49	[redacted]	£59,880
Paclitaxel	12,081	0.77	0.46	[redacted]	0.49	[redacted]	£55,546
Methotrexate	11,736	0.77	0.46	[redacted]	0.49	[redacted]	£56,616
'Utility optimistic'							
Nivolumab	[redacted]	1.26	[redacted]				
Docetaxel	10,682	0.77	0.41	[redacted]	0.49	[redacted]	£47,487
Paclitaxel	12,081	0.77	0.41	[redacted]	0.49	[redacted]	£44,050
Methotrexate	11,736	0.77	0.41	[redacted]	0.49	[redacted]	£44,899

Abbreviations: ICER: incremental cost-effectiveness ratio; LY(G): life years (gained); PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Table 5: Cost-effectiveness results from revised base case analysis – piecewise lognormal approach with 36-week cut-off point (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
'Utility pessimistic'							
Nivolumab	[redacted]	1.37	[redacted]				
Docetaxel	10,777	0.82	0.49	[redacted]	0.55	[redacted]	£54,213
Paclitaxel	12,176	0.82	0.49	[redacted]	0.55	[redacted]	£50,312
Methotrexate	11,831	0.82	0.49	[redacted]	0.55	[redacted]	£51,275
'Utility optimistic'							
Nivolumab	[redacted]	1.37	[redacted]				

Docetaxel	10,777	0.82	0.43	[redacted]	0.55	[redacted]	£43,013
Paclitaxel	12,176	0.82	0.43	[redacted]	0.55	[redacted]	£39,918
Methotrexate	11,831	0.82	0.43	[redacted]	0.55	[redacted]	£40,682

Abbreviations: ICER: incremental cost-effectiveness ratio; LY(G): life years (gained); PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Table 6: Cost-effectiveness results from revised base case analysis – piecewise lognormal approach with 48-week cut-off point (with PAS for nivolumab)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
'Utility pessimistic'							
Nivolumab	[redacted]	1.10	[redacted]				
Docetaxel	10,499	0.68	0.41	[redacted]	0.41	[redacted]	£69,371
Paclitaxel	11,899	0.68	0.41	[redacted]	0.41	[redacted]	£64,308
Methotrexate	11,553	0.68	0.41	[redacted]	0.41	[redacted]	£65,558
'Utility optimistic'							
Nivolumab	[redacted]	1.10	[redacted]				
Docetaxel	10,499	0.68	0.37	[redacted]	0.41	[redacted]	£55,602
Paclitaxel	11,899	0.68	0.37	[redacted]	0.41	[redacted]	£51,544
Methotrexate	11,553	0.68	0.37	[redacted]	0.41	[redacted]	£52,546

Abbreviations: ICER: incremental cost-effectiveness ratio; LY(G): life years (gained); PAS: Patient Access Scheme; QALY: quality-adjusted life year.

2. Summary of ICERs presented thus far

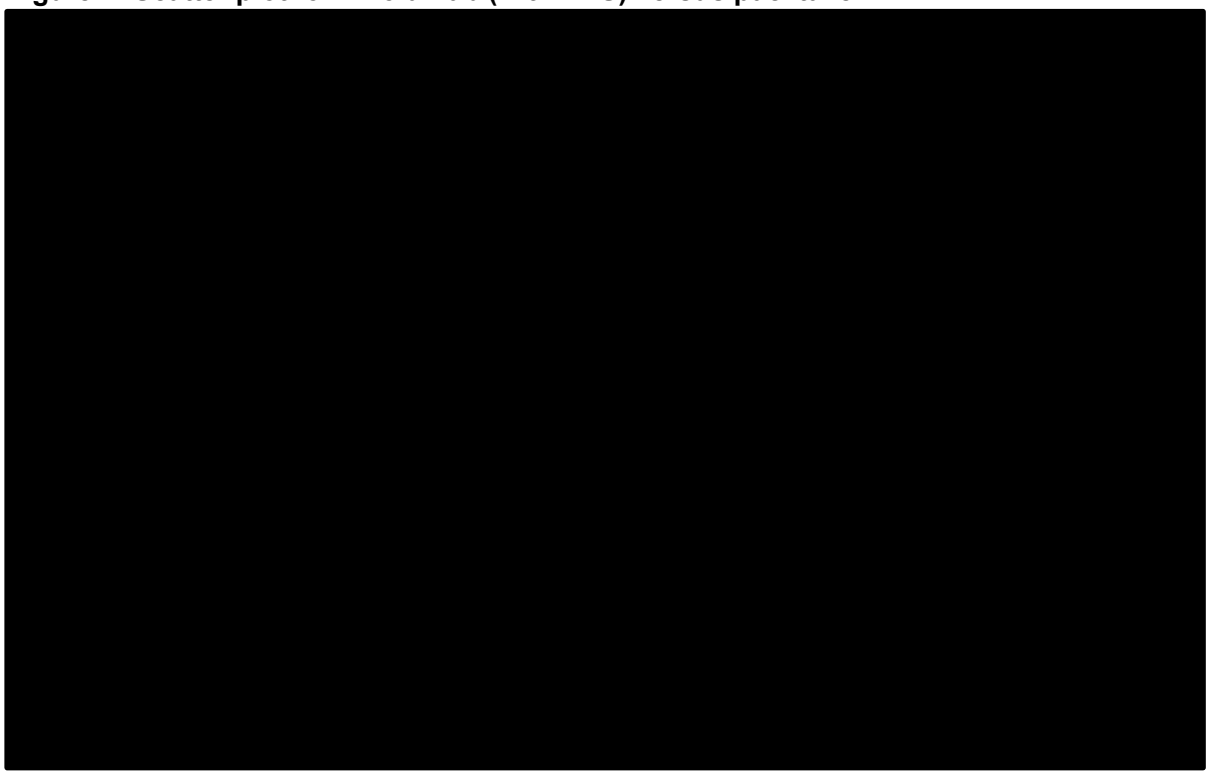
Figures 1 to 3 present scatter plots of incremental costs and QALYs for nivolumab (with PAS) versus each of the relevant comparators. These figures illustrate the range of cost-effectiveness estimates that have been considered thus far as part of this appraisal and show the discrepancy in ICERs between those derived from analyses conducted using the Committee-preferred assumptions, as described in the ACD, and those from all other analyses considered to date, including the company submission and the analyses preferred by the ERG (see Table 7 for full details of the analyses presented).

Results from the revised base case show nivolumab (with PAS) to plausibly be in the range of cost-effectiveness versus each of the relevant comparators when considering the likely benefit of nivolumab in terms of utility (i.e. somewhere in between the 'utility pessimistic' and 'utility optimistic' estimates). In light of the information presented as part of this response, BMS urge the Committee to reconsider their current position with regards to the cost-effectiveness of nivolumab as an end-of-life medicine for a condition with a clear unmet medical need.

Figure 1: Scatter plot for nivolumab (with PAS) versus docetaxel

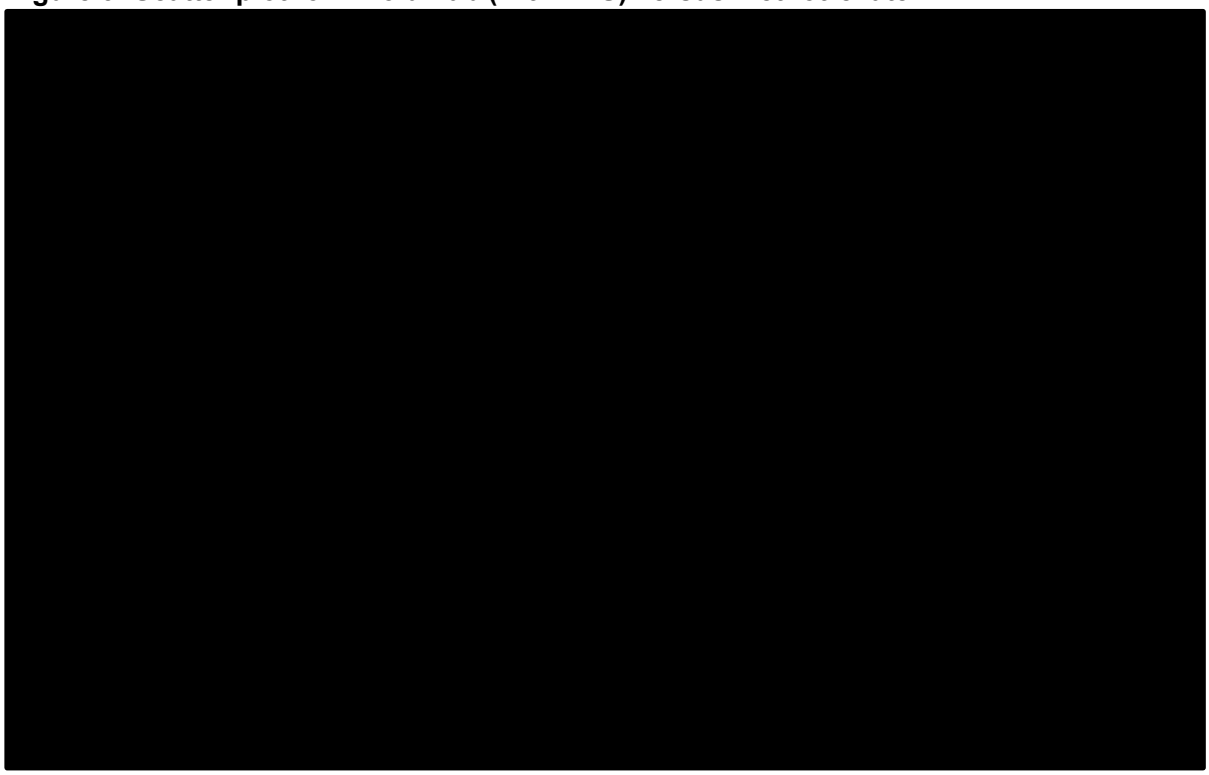
Abbreviations: ERG: Evidence Review Group; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Figure 2: Scatter plot for nivolumab (with PAS) versus paclitaxel



Abbreviations: ERG: Evidence Review Group; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Figure 3: Scatter plot for nivolumab (with PAS) versus methotrexate



Abbreviations: ERG: Evidence Review Group; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Table 7: List of analyses for scatter plots

Figure legend	Model assumptions for each analysis	Reference	Incremental results (range across comparators)		
			Costs (£)	QALYs	ICER (£ per QALY)
Company Submission	Fully parametric lognormal (both arms) Treatment-specific utility values With stopping rule	Table 5; Additional evidence submission	[redacted]	[redacted]	41,240 to 44,636
	Fully parametric lognormal (both arms) Treatment-specific utility values Without stopping rule	Table 7; Additional evidence submission	[redacted]	[redacted]	43,690 to 47,086
	Piecewise exponential – 20 weeks (IC) Fully parametric lognormal (nivolumab) Treatment-specific utility values With stopping rule	Table 19; Additional evidence submission	[redacted]	[redacted]	39,287 to 42,503
	Piecewise exponential – 20 weeks (IC) Fully parametric lognormal (nivolumab) Treatment-specific utility values Without stopping rule	Table 21; Additional evidence submission	[redacted]	[redacted]	41,606 to 44,823
	Fully parametric lognormal (both arms) Treatment-specific utility values With stopping rule Treatment waning effect – 5 years	Table 25; Additional evidence submission	[redacted]	[redacted]	45,674 to 49,465
	Fully parametric lognormal (both arms) Treatment-specific utility values Without stopping rule Treatment waning effect – 5 years	Table 27; Additional evidence submission	[redacted]	[redacted]	48,408 to 52,200
	Piecewise lognormal – 20 weeks (both arms) Treatment-specific utility values With stopping rule	Table 15; Additional evidence submission	[redacted]	[redacted]	41,571 to 45,008
	Piecewise lognormal – 20 weeks (both arms) Treatment-specific utility values Without stopping rule	Table 17; Additional evidence submission	[redacted]	[redacted]	44,050 to 47,487

Figure legend	Model assumptions for each analysis	Reference	Incremental results (range across comparators)		
			Costs (£)	QALYs	ICER (£ per QALY)
ERG response	As per Company Submission base case, except: Without stopping rule Pneumonitis included Treatment-independent modelling of subsequent therapies	Table 5; ERG addendum to review of additional evidence submission	[redacted]	[redacted]	44,007 to 47,419
Committee preferred	Piecewise exponential – 20 weeks (both arms) Treatment-specific utility values Without stopping rule	Section 4.19; ACD	[redacted]	[redacted]	66,727 to 72,037
	Piecewise exponential – 48 weeks (both arms) Treatment-specific utility values Without stopping rule	Table 5; ERG addendum to review of additional evidence submission	[redacted]	[redacted]	65,628 to 70,849
	Fully parametric lognormal (both arms) Disutility for patients who discontinue nivolumab[a] Without stopping rule		[redacted]	[redacted]	61,770 to 66,560
Response to ACD: lognormal pessimistic	Fully parametric lognormal (both arms) Treatment-independent utility values Without stopping rule	Table 3; This document	[redacted]	[redacted]	52,833 to 56,940
Response to ACD: lognormal optimistic	Fully parametric lognormal (both arms) Treatment-specific utility values Without stopping rule	Table 3; This document	[redacted]	[redacted]	43,690 to 47,086
Response to ACD: lognormal piecewise pessimistic	Piecewise lognormal – 20 weeks (both arms) Treatment-independent utility values Without stopping rule	Table 4; This document	[redacted]	[redacted]	55,546 to 59,880
	Piecewise lognormal – 48 weeks (both arms) Treatment-independent utility values Without stopping rule	Table 6; This document	[redacted]	[redacted]	64,308 to 69,371
	Piecewise lognormal – 20 weeks (both arms) Treatment-specific utility values Without stopping rule	Table 4; This document	[redacted]	[redacted]	44,050 to 47,487

Figure legend	Model assumptions for each analysis	Reference	Incremental results (range across comparators)		
			Costs (£)	QALYs	ICER (£ per QALY)
Response to ACD: lognormal piecewise optimistic	Piecewise lognormal – 48 weeks (both arms) Treatment-specific utility values Without stopping rule	Table 6; This document	[redacted]	[redacted]	51,544 to 55,602

[a] 'Corrected' ICERs based on the use of the treatment-independent utility values estimated by the ERG are presented in Part 2 of the main ACD response.

Abbreviations: ACD: Appraisal Consultation Document; ERG: Evidence Review Group; IC: investigator's choice; ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission

ID971: Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy

May 2017

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Generic Name: Nivolumab

Brand Name: Opdivo®

Disease area: Squamous cell carcinoma of the head and neck (SCCHN)

Indication: SCCHN in adults progressing on or after platinum-based therapy

Nivolumab is currently being appraised by NICE for use in this indication as part of ID971: Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy.

3.2 Please outline the rationale for developing the patient access scheme. Please describe the type of patient access scheme, as defined by the PPRS.

In cost-effectiveness analyses for nivolumab versus the relevant comparators in this indication (docetaxel, paclitaxel and methotrexate), the incremental cost-effectiveness ratio (ICER) is higher than NICE's anticipated willingness to pay threshold for technologies that meet the end-of-life criteria (see ID971 Appraisal Consultation Document [ACD]), when using either:

- List price for nivolumab
- The Patient Access Scheme (PAS) of a simple discount to nivolumab presented in the original Company Evidence Submission

BMS is therefore proposing a revised simple discount scheme to meet NICE cost-effectiveness criteria.

3.3 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these been chosen?

- How are the criteria measured and why have the measures been chosen?

The revised PAS for nivolumab will apply to all patients covered by NICE guidance for nivolumab as a treatment for adult patients with SCCHN who have progressed on or after platinum-based therapy [i.e. ID971].

If the NICE committee recommends nivolumab for the SCCHN indication [ID971], then this simple PAS will also apply across all the other licensed indications of nivolumab (melanoma monotherapy [TA384], and regimen [TA400], and renal cell carcinoma (RCC) [TA417]), for which NICE has already given a positive recommendation.

Melanoma and renal cell cancer 'credit'

BMS believe that the impact of wider benefit to the NHS from this revised PAS should be taken into account, given that the increased simple discount being proposed will apply across all indications. This impact was acknowledged in the recent appraisal of pembrolizumab and included in Section 4.18 of the Final Appraisal Determination for pembrolizumab in NSCLC [TA428], which states,

"[the committee] *was also aware that there would be a wider benefit to the NHS because the simple discount agreed in the patient access scheme would apply across all indications."*

Nivolumab has already been appraised and recommended by NICE for melanoma [TA384 and TA400] and RCC [TA417]. All of these were recommended with a discount of less than [redacted]%, as is being proposed here (see Table 1).

Table 1: Credit gained from existing indications

Indication of Nivolumab	Cost-effective PAS Level	Proposal Selling Discount	'Credit' Percentage
Melanoma	0%	[redacted]	[redacted]
RCC	[redacted]	[redacted]	[redacted]

RCC: renal cell carcinoma.

Under the current proposal, both melanoma and RCC would be available with a [redacted] discount, resulting in a lower treatment costs for these indications. To account for these savings, the melanoma and RCC cost-effectiveness models were run at their cost-effective PAS levels (0% and [redacted], respectively; see Table 2 to Table 4) and then again at [redacted] (see Table 5 to Table 7). The

difference in cost per melanoma or RCC patient treated with nivolumab was then subtracted from the incremental costs in the models and multiplied by the nivolumab treated patient populations for the respective indications, to estimate the total value to the NHS of the increased PAS (see Table 8).

ICERs for NICE approved indications at their approved prices

Table 2: Melanoma (BRAF –ve) at 0%

First-line (BRAF -ve)	Totals			Incremental (Nivo vs. comparator)			Cost per QALY (Nivo vs comparator)
Treatment Arm	Costs	QALYs	LY	Costs	QALYs	LY	
Nivolumab plus Ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: Melanoma (BRAF +ve) at 0%

First-line (BRAF +ve)	Totals			Incremental (Nivo vs. comparator)			Cost per QALY (Nivo vs comparator)
Treatment Arm	Costs	QALYs	LY	Costs	QALYs	LY	
Nivolumab plus Ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: RCC at [redacted]%

2nd Line RCC	Totals			Incremental (Nivo vs. comparator)			Cost per QALY (Nivo vs comparator)
Treatment Arm	Costs	QALYs	LY	Costs	QALYs	LY	
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICERs for NICE approved indications with the revised PAS

Table 5: Melanoma (BRAF –ve) at [redacted]%

First-line (BRAF -ve)	Totals			Incremental (Nivo vs. comparator)			Cost per QALY (Nivo vs comparator)
Treatment Arm	Costs	QALYs	LY	Costs	QALYs	LY	
Nivolumab plus Ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: Melanoma (BRAF +ve) at [redacted]%

First-line (BRAF +ve)	Totals			Incremental (Nivo vs. comparator)			Cost per QALY (Nivo vs comparator)
Treatment Arm	Costs	QALYs	LY	Costs	QALYs	LY	
Nivolumab plus Ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: RCC at [redacted]%

2nd Line RCC	Totals			Incremental (Nivo vs. comparator)			Cost per QALY (Nivo vs comparator)
Treatment Arm	Costs	QALYs	LY	Costs	QALYs	LY	
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8: Patient population estimated to receive nivolumab

	2016	2017	2018	2019	2020
BRAF -ve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRAF +ve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total estimated value of the additional PAS to melanoma and RCC

By combining the average per patient saving (accrued due to the increase in the PAS) with the total patients estimated to be treated for each indication (combining both the eligible patient population and the expected market share) the total value of the additional discount to the NHS is estimated (see Table 9).

The impact of these total savings (per SCCHN patient) has been included in the cost-effectiveness analysis presented in Section 4.11.

Table 9: Total value of additional discount

	Melanoma BRAF -ve	Melanoma BRAF +ve	RCC	Total
Savings per patient	[redacted]	[redacted]	[redacted]	
Population saving per indication	[redacted]	[redacted]	[redacted]	
Total Savings				[redacted]

3.4 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

As noted above, BMS is proposing a simple discount PAS, allowing the drug to meet NICE cost-effectiveness criteria. This would apply to all patients in the population specified.

3.5 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Not applicable

3.6 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

A simple confidential [redacted] discount will be offered for nivolumab; therefore, no rebates are to be calculated or paid.

3.7 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

A fixed price (which will not vary with any change to the UK list price) is proposed, if list price is reduced to below the fixed PAS price then this would become the new price point for the PAS.

The proposed discount will be reflected on the original invoice for direct supply of nivolumab to NHS Trusts. For supply through homecare companies, Bristol-Myers Squibb Pharmaceuticals Ltd will rebate homecare companies the difference between list price and PAS price based on number of nivolumab packs sold via homecare. The homecare provider will invoice NHS trusts for nivolumab at the PAS price. We believe this is consistent with existing financial flows within NHS.

3.8 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable

3.9 Please provide details of the duration of the scheme.

There are no plans or clauses or circumstances where BMS will withdraw the proposed nivolumab PAS nationally where the scheme is being operated with normal procurement practices and under standard terms and conditions. BMS will look to consult with stakeholders (including DH and PASLU) on any scheme changes and will participate in any required exit arrangement from the nivolumab PAS should these be required.

In the event of negative NICE advice for ID971, the proposed PAS will not apply.

3.10 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

Not applicable

3.11 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

PAS agreement form (including terms and conditions): This is where BMS Standard Terms and Conditions will be used for supply of nivolumab.

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

Not applicable

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Results of the revised model are presented in Sections 4.7 and 4.8 using the latest model assumptions as described in the Company ACD response (May 2017).

Full details of model assumptions and changes are described in Section 4.3 below.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

In the economic model, the PAS is incorporated as a simple discount to the cost per vial for nivolumab ('Treatment Costs' sheet in the Excel model). The level of discount to be applied to nivolumab in the model can specified by the user by entering the desired percentage into the input cells labelled 'Discount' for both nivolumab vial sizes.

Model assumptions and changes

As highlighted in the Company ACD response, BMS maintain that the approach to extrapolating overall survival (OS) preferred by the Appraisal Committee (i.e. piecewise exponential) is not appropriate given the evidence available from other nivolumab indications and clinical expert opinion. BMS instead believe that alternative extrapolation approaches (i.e. fully parametric lognormal) offer more plausible estimates of the long-term survival with nivolumab. Cost-effectiveness results have therefore been presented in Sections 4.7 and 4.8 from analyses that incorporate what BMS consider to represent the most plausible estimates of OS for nivolumab (i.e. fully parametric lognormal), as was presented in the Company ACD response.

In response to the ACD, BMS agreed with the Committee that the use of treatment-independent utility values may not adequately capture the additional quality-of-life benefit that has been demonstrated with nivolumab versus the comparators (see Section 4.16 of the ACD). In order to reflect the Committee's conclusion that the most appropriate utility values are likely to lie between the treatment-specific and treatment-independent utility estimates, cost-effectiveness results are presented in Sections 4.7 and 4.8 using both treatment-specific ('utility optimistic') and treatment-independent ('utility pessimistic') utility values, as done in the Company ACD response.

The results presented in Sections 4.7 and 4.8 also incorporate the Committee's preferred assumptions of:

- No clinical stopping rule
- Docetaxel 75 mg/m^2 once every three weeks

These assumptions were also incorporated in the model used for the Company ACD response. All other inputs and model assumptions remain the same.

Results from additional analyses can be provided on request.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The PAS is not related to clinical effectiveness.

Clinical effectiveness data used in the economic model has not changed since data from the latest database lock of CheckMate 141 was incorporated in to

the model as part of the Company Additional Evidence Submission (February 2017).

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

Not applicable

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Utility pessimistic

Table 10: Base-case cost-effectiveness results – utility pessimistic (without PAS)

	Nivolumab	Docetaxel	Paclitaxel	Methotrexate
Intervention cost (£)	[redacted]	88	182	129
Treatment administration (£)	[redacted]	653	1,959	1,959
Treatment monitoring costs (£)	[redacted]	775	775	775
Subsequent treatments (£)	[redacted]	563	563	270
AE costs (£)	[redacted]	651	651	651
PF cost (£)	[redacted]	703	703	703
PD cost (£)	[redacted]	6,810	6,810	6,810
One-off progression costs (£)	[redacted]	239	239	239
Total costs (£)	[redacted]	10,482	11,881	11,536
Difference in total costs (£)	-	[redacted]	[redacted]	[redacted]
LYG	1.20	0.67	0.67	0.67
LYG difference	-	0.52	0.52	0.52
QALYs	[redacted]	0.41	0.41	0.41
QALY difference	-	[redacted]	[redacted]	[redacted]
ICER (£ per QALY)	-	[redacted]	[redacted]	[redacted]

LYG: life-year gained; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

Table 11: Base-case cost-effectiveness results – utility pessimistic (with revised PAS)

	Nivolumab	Docetaxel	Paclitaxel	Methotrexate
Intervention cost (£)	[redacted]	88	182	129
Treatment administration (£)	[redacted]	653	1,959	1,959
Treatment monitoring costs (£)	[redacted]	775	775	775
Subsequent treatments (£)	[redacted]	563	563	270
AE costs (£)	[redacted]	651	651	651
PF cost (£)	[redacted]	703	703	703
PD cost (£)	[redacted]	6,810	6,810	6,810
One-off progression costs (£)	[redacted]	239	239	239
Total costs (£)	[redacted]	10,482	11,881	11,536
Difference in total costs (£)	-	[redacted]	[redacted]	[redacted]
LYG	1.20	0.67	0.67	0.67
LYG difference	-	0.52	0.52	0.52
QALYs	[redacted]	0.41	0.41	0.41
QALY difference	-	[redacted]	[redacted]	[redacted]
ICER (£ per QALY)	-	£50,822	£46,715	£47,729

LYG: life-year gained; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

Utility optimistic

Table 12: Base-case cost-effectiveness results – utility optimistic (without PAS)

	Nivolumab	Docetaxel	Paclitaxel	Methotrexate
Intervention cost (£)	[redacted]	88	182	129
Treatment administration (£)	[redacted]	653	1,959	1,959
Treatment monitoring costs (£)	[redacted]	775	775	775
Subsequent treatments (£)	[redacted]	563	563	270
AE costs (£)	[redacted]	651	651	651
PF cost (£)	[redacted]	703	703	703
PD cost (£)	[redacted]	6,810	6,810	6,810
One-off progression costs (£)	[redacted]	239	239	239
Total costs (£)	[redacted]	10,482	11,881	11,536
Difference in total costs (£)	-	[redacted]	[redacted]	[redacted]
LYG	1.20	0.67	0.67	0.67
LYG difference	-	0.52	0.52	0.52
QALYs	[redacted]	0.36	0.36	0.36
QALY difference	-	[redacted]	[redacted]	[redacted]
ICER (£ per QALY)	-	[redacted]	[redacted]	[redacted]

LYG: life-year gained; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

Table 13: Base-case cost-effectiveness results – utility optimistic (with revised PAS)

	Nivolumab	Docetaxel	Paclitaxel	Methotrexate
Intervention cost (£)	[redacted]	88	182	129
Treatment administration (£)	[redacted]	653	1,959	1,959
Treatment monitoring costs (£)	[redacted]	775	775	775
Subsequent treatments (£)	[redacted]	563	563	270
AE costs (£)	[redacted]	651	651	651
PF cost (£)	[redacted]	703	703	703
PD cost (£)	[redacted]	6,810	6,810	6,810
One-off progression costs (£)	[redacted]	239	239	239
Total costs (£)	[redacted]	10,482	11,881	11,536
Difference in total costs (£)	-	[redacted]	[redacted]	[redacted]
LYG	1.20	0.67	0.67	0.67
LYG difference	-	0.52	0.52	0.52
QALYs	[redacted]	0.36	0.36	0.36
QALY difference	-	[redacted]	[redacted]	[redacted]
ICER (£ per QALY)	-	£42,027	£38,631	£39,469

LYG: life-year gained; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in Table 14.

Table 14: Base-case incremental results (without PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Utility pessimistic							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.41	[redacted]	0.52	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.41	[redacted]	0.52	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.41	[redacted]	0.52	[redacted]	[redacted]
Utility optimistic							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 15: Base-case incremental results (with revised PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Utility pessimistic							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.41	[redacted]	0.52	[redacted]	£50,822
Paclitaxel	11,881	0.67	0.41	[redacted]	0.52	[redacted]	£46,715
Methotrexate	11,536	0.67	0.41	[redacted]	0.52	[redacted]	£47,729
Utility optimistic							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	£42,027
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	£38,631
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	£39,469

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Deterministic sensitivity analyses were conducted by varying all parameters for which there were single input values into the model by ±20% of their mean value.

Tornado diagrams showing the top ten drivers of cost-effectiveness in the comparison of nivolumab versus docetaxel, paclitaxel and methotrexate are presented below for both 'utility pessimistic' and 'utility optimistic' analyses (with revised PAS for nivolumab).

Utility pessimistic

Figure 1: Tornado diagram of the ten most influential parameters: nivolumab versus docetaxel (with revised PAS for nivolumab) – utility pessimistic

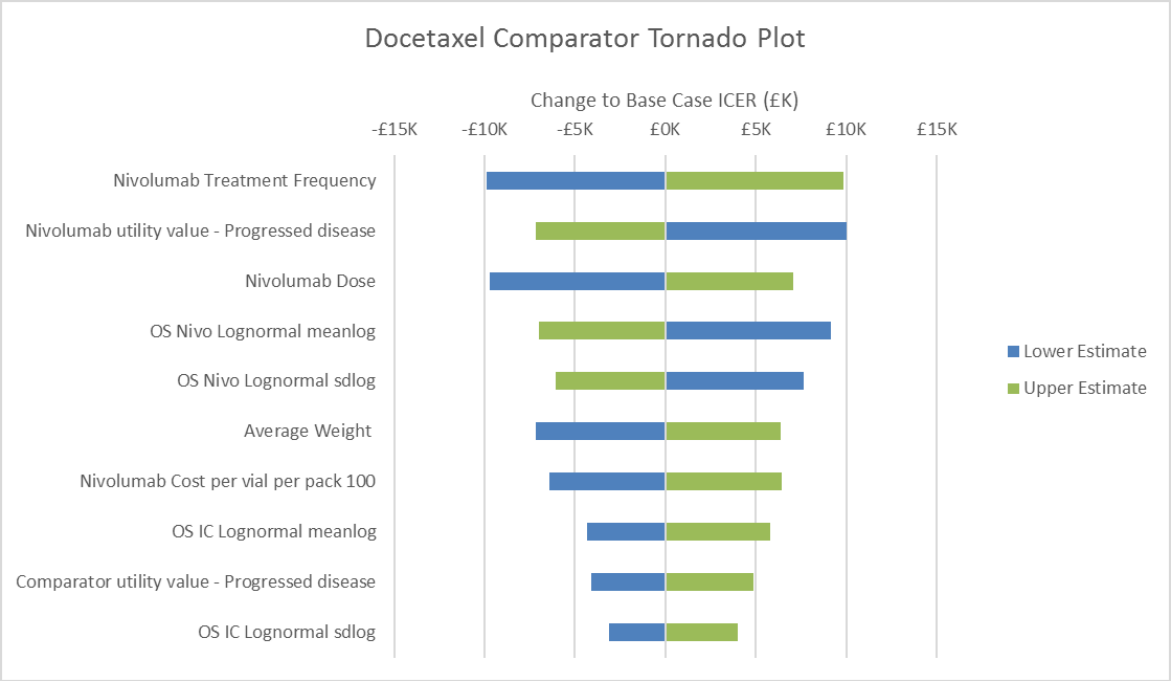


Figure 2: Tornado diagram of the ten most influential parameters: nivolumab versus paclitaxel (with revised PAS for nivolumab) – utility pessimistic

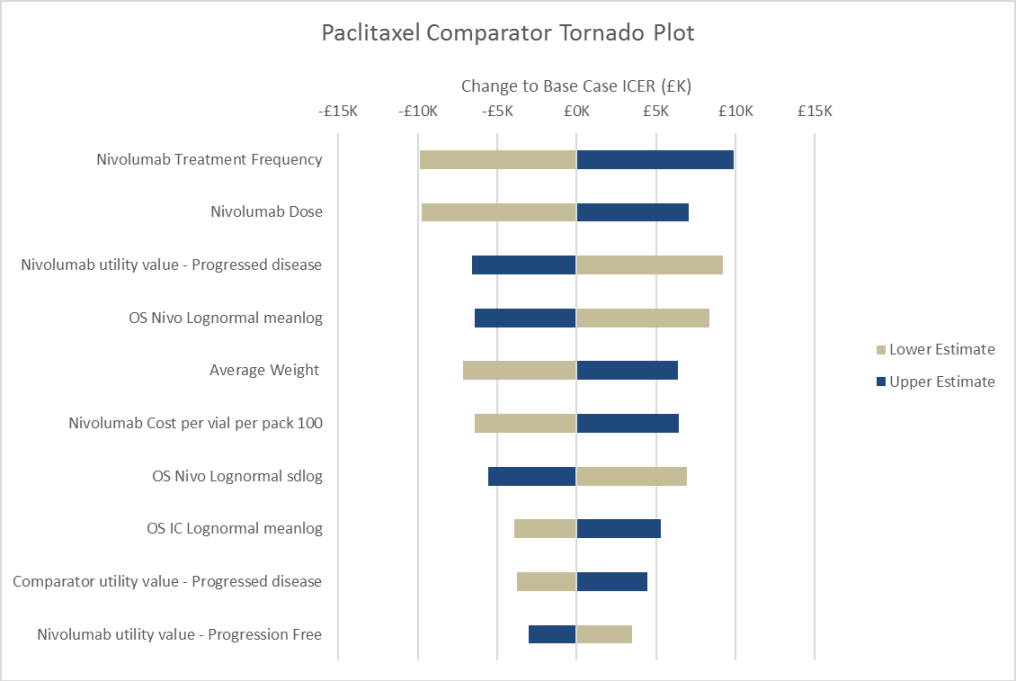
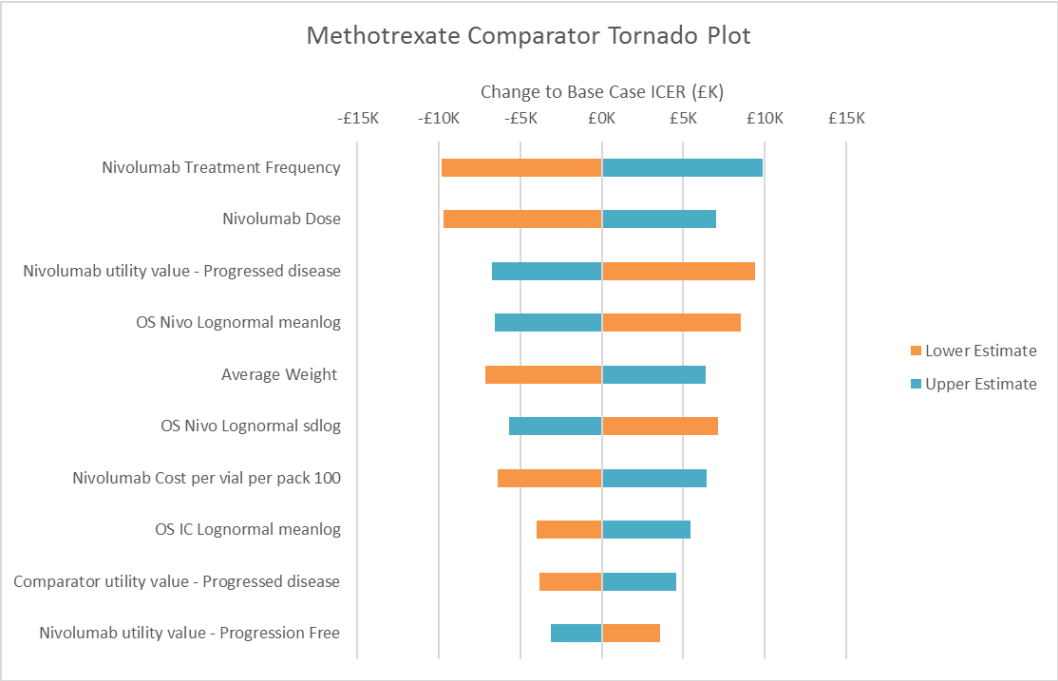


Figure 3: Tornado diagram of the ten most influential parameters: nivolumab versus methotrexate (with revised PAS for nivolumab) – utility pessimistic



Utility optimistic

Figure 4: Tornado diagram of the ten most influential parameters: nivolumab versus docetaxel (with revised PAS for nivolumab) – utility optimistic

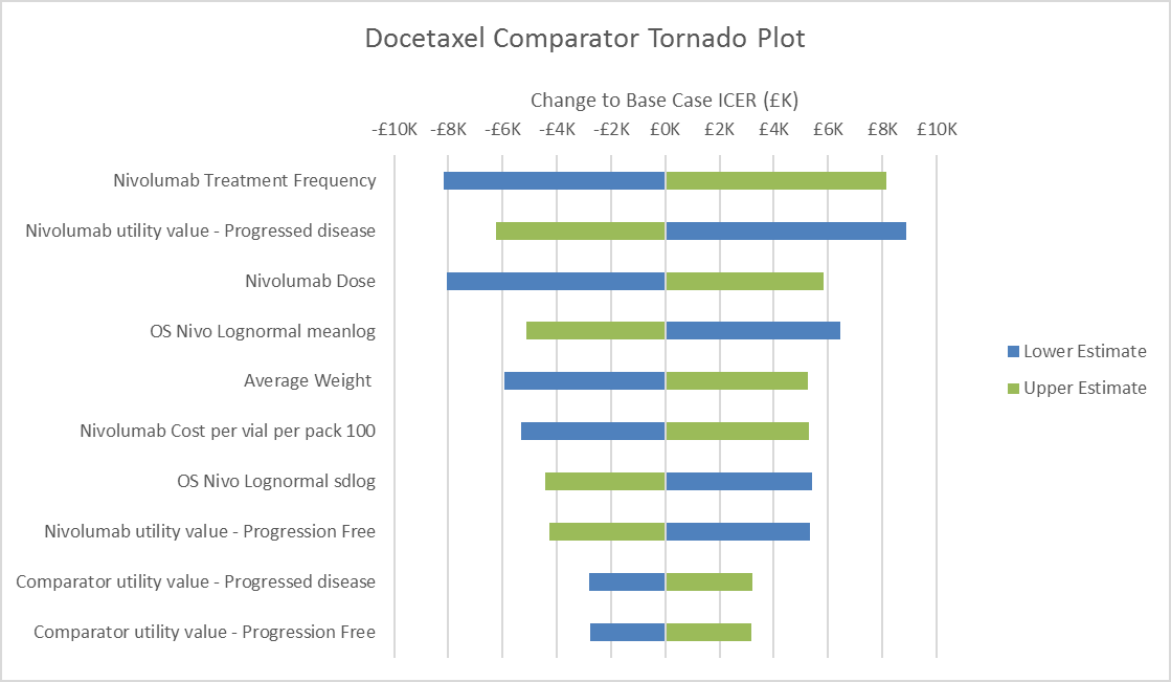


Figure 5: Tornado diagram of the ten most influential parameters: nivolumab versus paclitaxel (with revised PAS for nivolumab) – utility optimistic

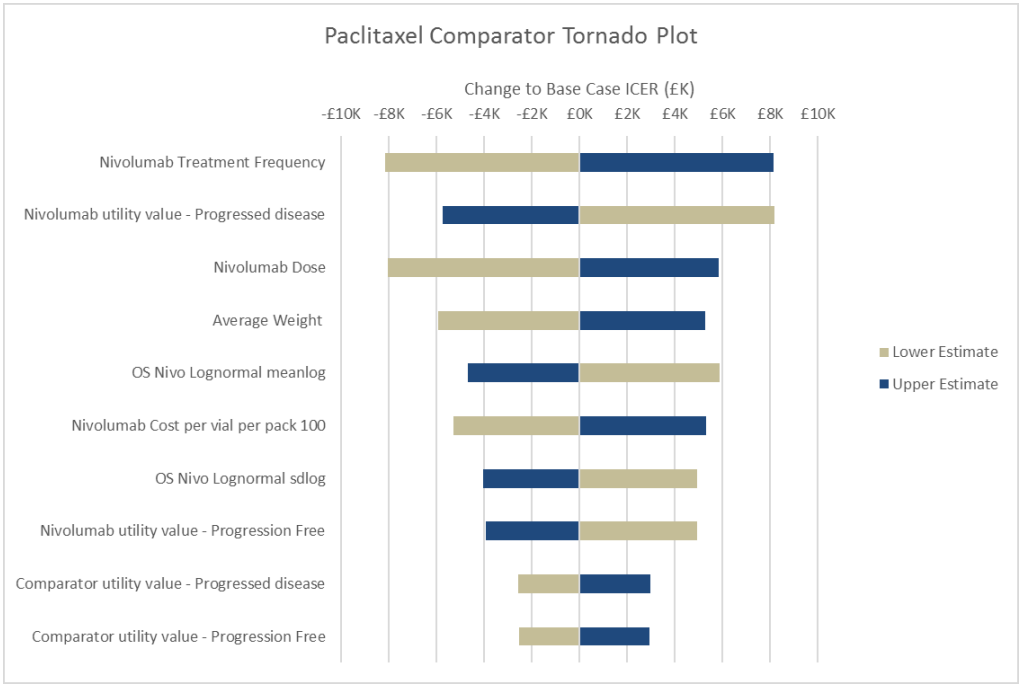
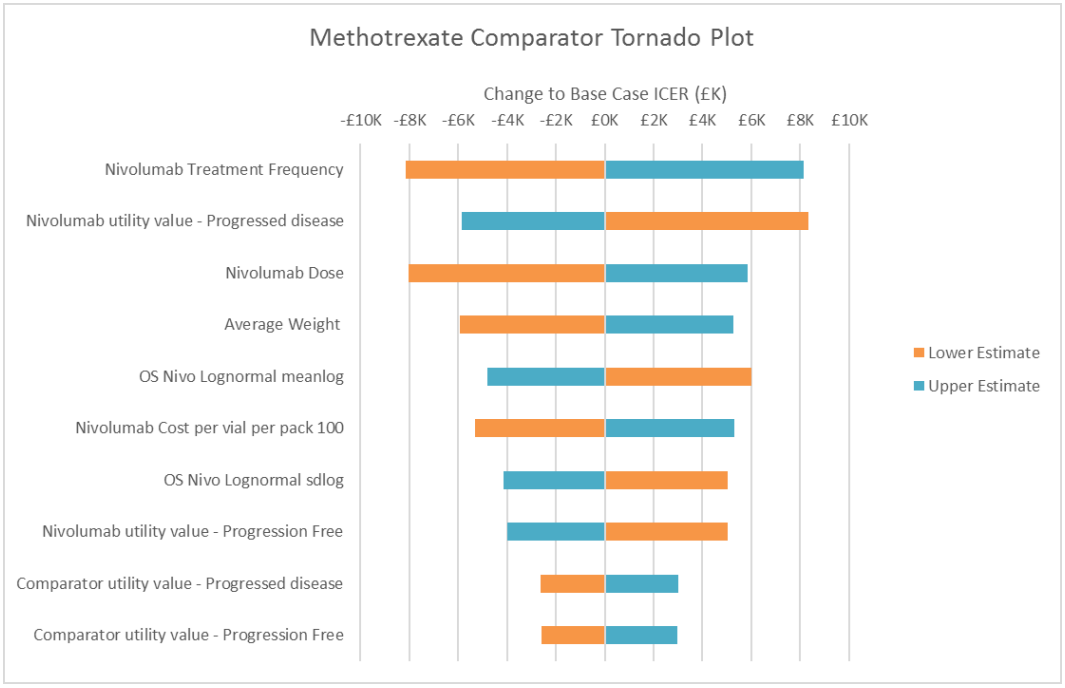


Figure 6: Tornado diagram of the ten most influential parameters: nivolumab versus methotrexate (with revised PAS for nivolumab) – utility optimistic



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

The incremental results from probabilistic sensitivity analyses (1,000 simulations) are presented in Table 16 (with revised PAS for nivolumab).

Scatter plots of incremental costs and QALYs for nivolumab (with revised PAS) versus docetaxel, paclitaxel and methotrexate are presented below for both 'utility pessimistic' and 'utility optimistic' analyses. Cost-effectiveness acceptability curves for nivolumab (with revised PAS) versus all comparators are also presented below.

Table 16: Probabilistic incremental results (with revised PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Utility pessimistic					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,539	0.41	[redacted]	[redacted]	£51,530
Paclitaxel	£12,001	0.41	[redacted]	[redacted]	£47,163
Methotrexate	£11,613	0.41	[redacted]	[redacted]	£48,321
Utility optimistic					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,525	0.37	[redacted]	[redacted]	£41,345
Paclitaxel	£11,918	0.37	[redacted]	[redacted]	£37,999
Methotrexate	£11,595	0.37	[redacted]	[redacted]	£38,771

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Utility pessimistic

Figure 7: Cost-effectiveness plane: probabilistic results for nivolumab versus docetaxel (with revised PAS for nivolumab) – utility pessimistic

Figure 8: Cost-effectiveness plane: probabilistic results for nivolumab versus paclitaxel (with revised PAS for nivolumab) – utility pessimistic

Figure 9: Cost-effectiveness plane: probabilistic results for nivolumab versus methotrexate (with revised PAS for nivolumab) – utility pessimistic

Figure 10: Cost-effectiveness acceptability curve for nivolumab versus all comparators (with revised PAS for nivolumab) – utility pessimistic

Utility optimistic

Figure 11: Cost-effectiveness plane: probabilistic results for nivolumab versus docetaxel (with revised PAS for nivolumab) – utility optimistic

Figure 12: Cost-effectiveness plane: probabilistic results for nivolumab versus paclitaxel (with revised PAS for nivolumab) – utility optimistic

Figure 13: Cost-effectiveness plane: probabilistic results for nivolumab versus methotrexate (with revised PAS for nivolumab) – utility optimistic

Figure 14: Cost-effectiveness acceptability curve for nivolumab versus all comparators (with revised PAS for nivolumab) – utility pessimistic

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Results of analyses using either 'utility pessimistic' or 'utility optimistic' estimates of utility have been presented above. As shown in Section 4.9, the utility values used are one of the major drivers of the model.

Additional scenario analyses have previously been conducted to explore various other structural assumptions and inputs (e.g. time horizon, choice of parametric survival distribution, adverse event disutility, subsequent therapy, treatment dosing and related patient characteristics). The results of these additional scenario analyses are presented in the Section 5.8.3 of the original Company Evidence Submission.

Impact of the melanoma and RCC credit on the BMS ICERs for SCCHN

Estimating the per patient value of the 'credit' in SCCHN

As noted in Section 3.3, BMS believe that the impact of wider benefit to the NHS from the revised PAS for nivolumab should be taken into account when considering the cost-effectiveness of nivolumab in SCCHN, given that the increased simple discount being proposed will apply across all indications.

To estimate the per patient saving which should be applied in SCCHN, BMS have taken the total value of the credit from RCC and melanoma (see Section 3.3 for derivation of this 'credit' value), and divided it by the total estimated patient numbers expected to be treated with nivolumab in SCCHN (quoted directly from the original manufacturer submission for ID971) (see Table 17). The relevant figures and tables estimating the SCCHN patient population are provided in the Company Appendix to this document, for ease of reference.

Table 17: Per patient value of discount in SCCHN

Total value of discount	Expected nivolumab-treated patient population[3]	Per patient value of discount in SCCHN
[redacted]	[redacted]	[redacted]

Impact on BMS ICERs for SCCHN

Table 18 presents the ICERs for the 'utility pessimistic' and 'utility optimistic' analyses in which the per patient 'credit' for SCCHN (arising from application of the revised PAS across all indications) has been applied to the incremental costs for nivolumab versus each of the comparators. Compared to the base case analysis in which this credit was not applied (see Table 15), the impact on the ICERs for SCCHN is a reduction of £19,683 and £16,277 for the utility pessimistic and utility optimistic analyses, respectively.

[3] 2018 is chosen as the reference year for consistency with the patient numbers in Year 2 and corresponds with the year of peak market share

Table 18: Base-case incremental results (with revised PAS and melanoma and RCC 'credit' applied)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£ per QALY)
Utility pessimistic							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.41	[redacted]	0.52	[redacted]	£31,139
Paclitaxel	11,881	0.67	0.41	[redacted]	0.52	[redacted]	£27,032
Methotrexate	11,536	0.67	0.41	[redacted]	0.52	[redacted]	£28,046
Utility optimistic							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,482	0.67	0.36	[redacted]	0.52	[redacted]	£25,750
Paclitaxel	11,881	0.67	0.36	[redacted]	0.52	[redacted]	£22,354
Methotrexate	11,536	0.67	0.36	[redacted]	0.52	[redacted]	£23,192

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

The PAS is not dependent on any clinical variables.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 33). If you are submitting the patient access scheme at the end of the appraisal process, you must

include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 19: Summary of results showing the impact of patient access scheme on ICERs for scenarios

ICERs	Vs. Docetaxel		Vs. Paclitaxel		Vs. Methotrexate	
	Without PAS	With PAS	Without PAS	With PAS	Without PAS	With PAS
Base case (Utility pessimistic)	[redacted]	£50,822	[redacted]	£46,715	[redacted]	£47,729
Base case (Utility optimistic)	[redacted]	£42,027	[redacted]	£38,631	[redacted]	£39,469
With melanoma and RCC credit (Utility pessimistic)	N/A	£31,139	N/A	£27,032	N/A	£28,046
With melanoma and RCC credit (Utility optimistic)	N/A	£25,750	N/A	£22,354	N/A	£23,192

ICER: incremental cost-effectiveness ratio.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

PAS agreement form (including terms and conditions): This is the BMS Standard Terms and Conditions which will be used for supplying nivolumab

5.2 Appendix B: Details of outcome-based schemes

Not applicable

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the

additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

5.3 Company Appendix

Figure 15: Eligible population for nivolumab as a treatment for adult patients with R/M SCCHN who have progressed after platinum-based therapy

(Source: Table 82 from Company Evidence Submission)

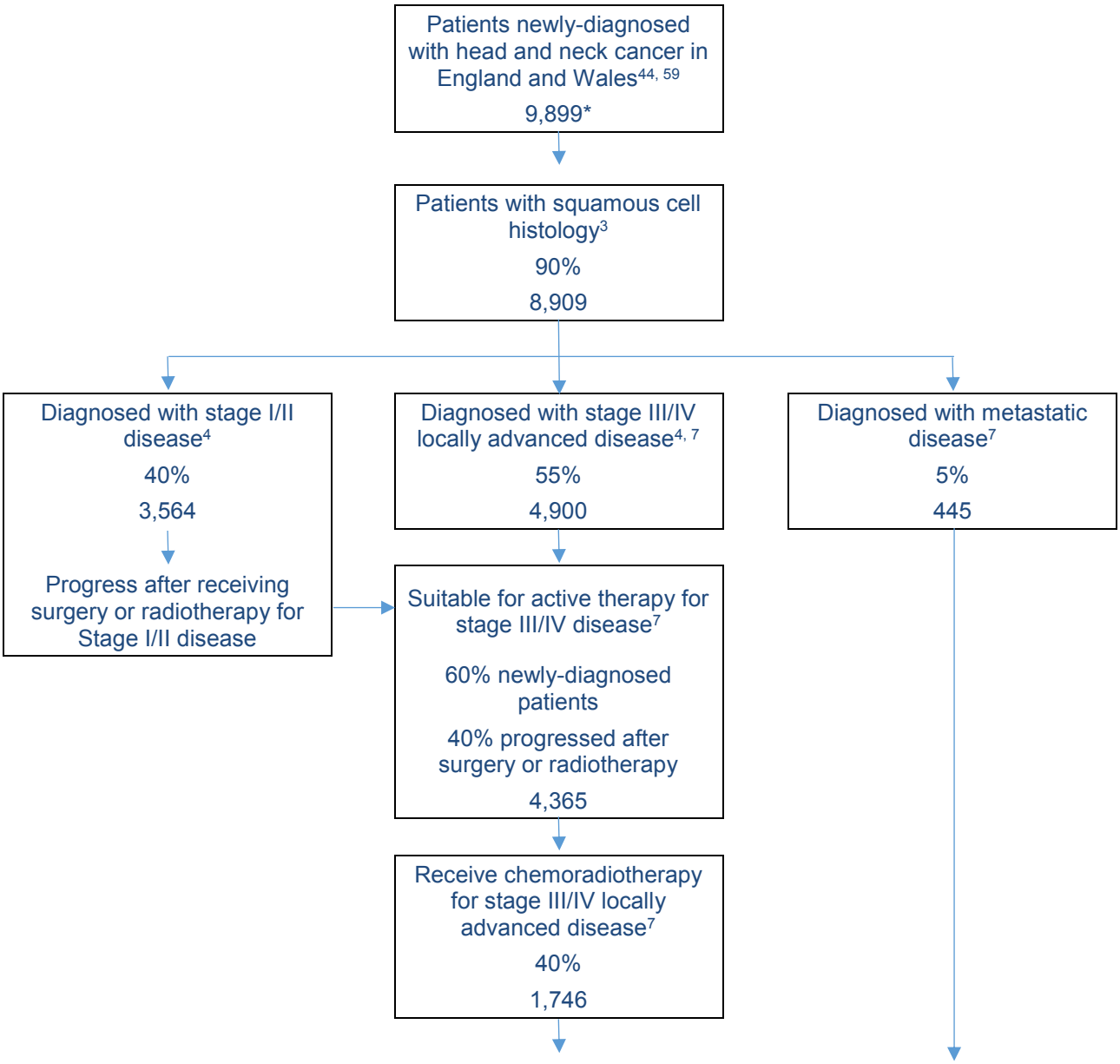
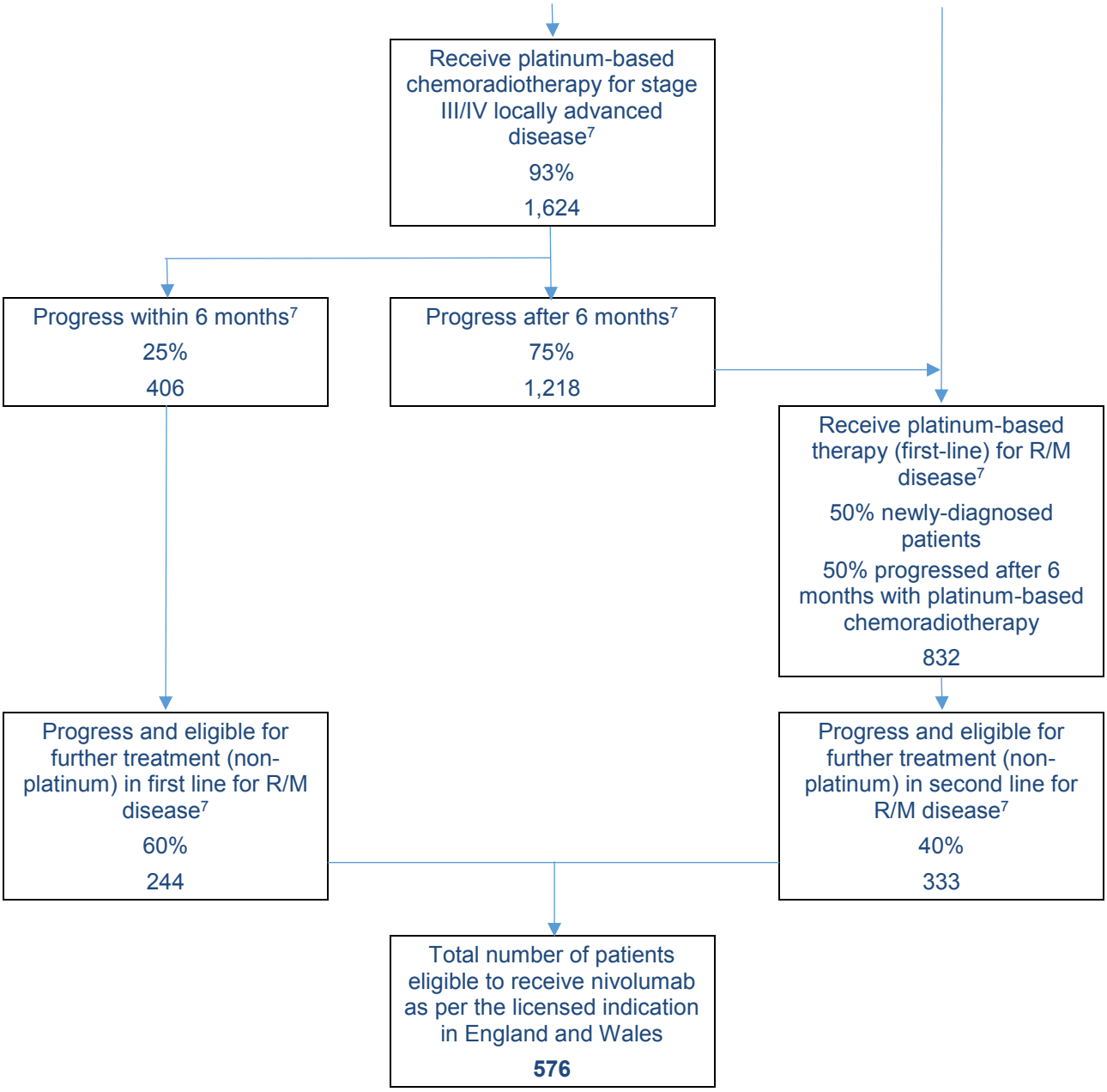


Figure continued.



* Includes cases classified under ICD10 codes: C00 to C14 and C30 to C32. Individual C00–C97 codes refer to diseases classified as 'malignant neoplasms' by the World Health Organisation in the ICD-10.

Abbreviations: ICD: International Classification of Diseases; N/A: not applicable; R/M: recurrent or metastatic; SCCHN: squamous-cell carcinoma of the head and neck.

Table 20: Number of patients receiving each therapy – NHS with nivolumab

(Source: Table 82 from Bristol-Myers Squibb Company Submission)

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy: critique on BMS submission of May 11th 2017

Produced by

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

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Declared competing interests of the authors
None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Nigel Armstrong acted as project lead as well as systematic reviewer and health economist on this assessment, critiqued the clinical effectiveness methods and evidence as well as the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Xavier Pouwels, Remziye Zaim and Ching-Yun Wei acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Robert Wolff and Rob Riemsma acted as systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore and Maiwenn Al acted as health economists on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

1. Approach to the estimation of overall survival

As stated in the original ERG report: the ERG considered the statistical methods used by the company for selecting the distributions for the time-to-event models as appropriate and consistent with the NICE DSU Technical Support Document for survival analysis. {Latimer, 2011 (updated 2013) #132}

The company argues that the piecewise exponential is not appropriate given that:

1. It is not consistent with clinical opinion indicating that "Any estimate of likely survival should include a long-term, durable plateau around 7–15%."
2. The piecewise approach results in logical inconsistencies
3. The exponential distribution is contradictory to decreasing hazard of death found for nivolumab in other indications

The ERG agrees that the piecewise approach results in logical inconsistencies. This is illustrated in the Figures 1 and 2 below showing overall survival (OS), progression free survival (PFS) and time to treatment discontinuation (TTD) for nivolumab and the investigators choice (IC) respectively. To illustrate the overlap, Figures focussing on the tails of the curves were added as well. For nivolumab the piecewise OS curves starts to cross with the PFS and TTD curves after 55 and 87 months respectively (all piecewise OS curves cross both PFS and TTD. For IC, the piecewise OS curves starts to cross with the PFS curve after 155 months while the TTD curve remains consistent with the OS curve. It should be noted that for the IC, the piecewise OS curves with a 48 weeks cut-off does not cross the PFS or TTD curves.

Regarding the company's argument that the exponential distribution is contradictory to decreasing hazard of death found for nivolumab in other indications, the ERG believes it is difficult to make inferences from other diseases. Therefore, in this case it might be useful to examine the statistical fit and clinical plausibility of other candidate distributions for the parametric time-to-event model. When adopting a piecewise model this might however lead to ambiguous results given this should be performed for each cut off value that is considered relevant potentially providing different alternatives (from which it might be difficult to choose).

[redacted]**Figure 1: Nivolumab OS, PFS and TTD**

[redacted]

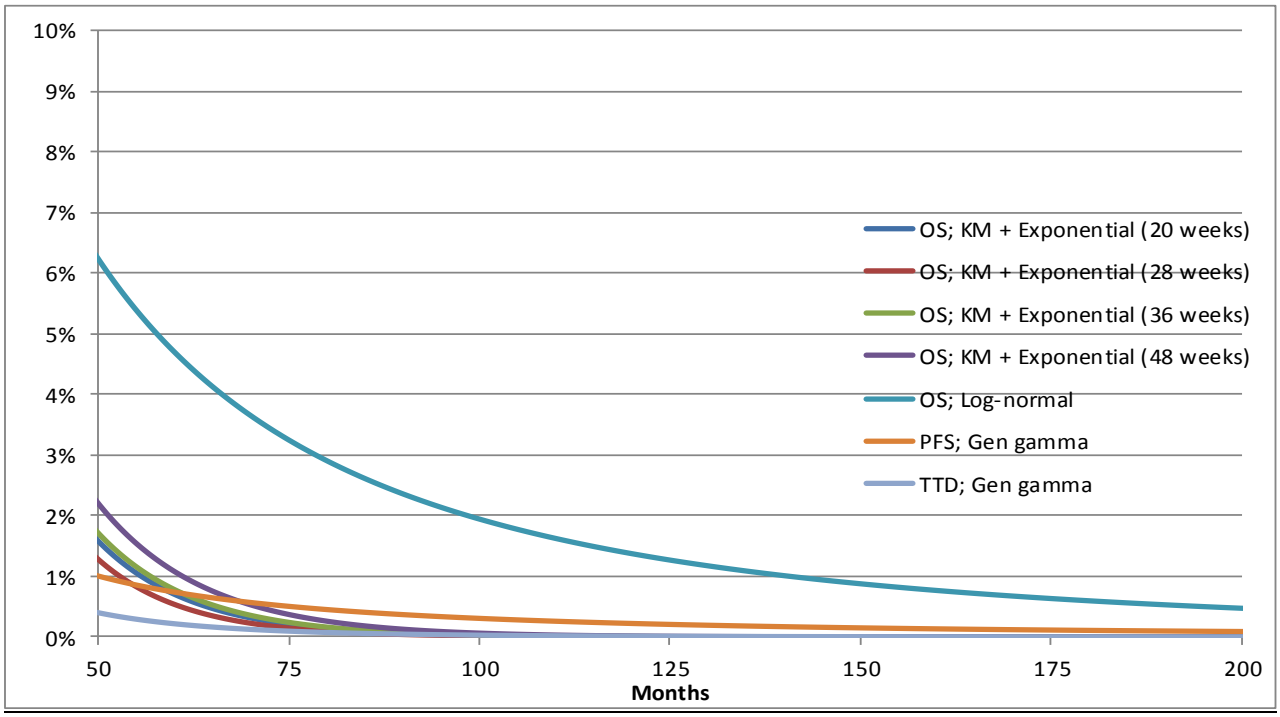
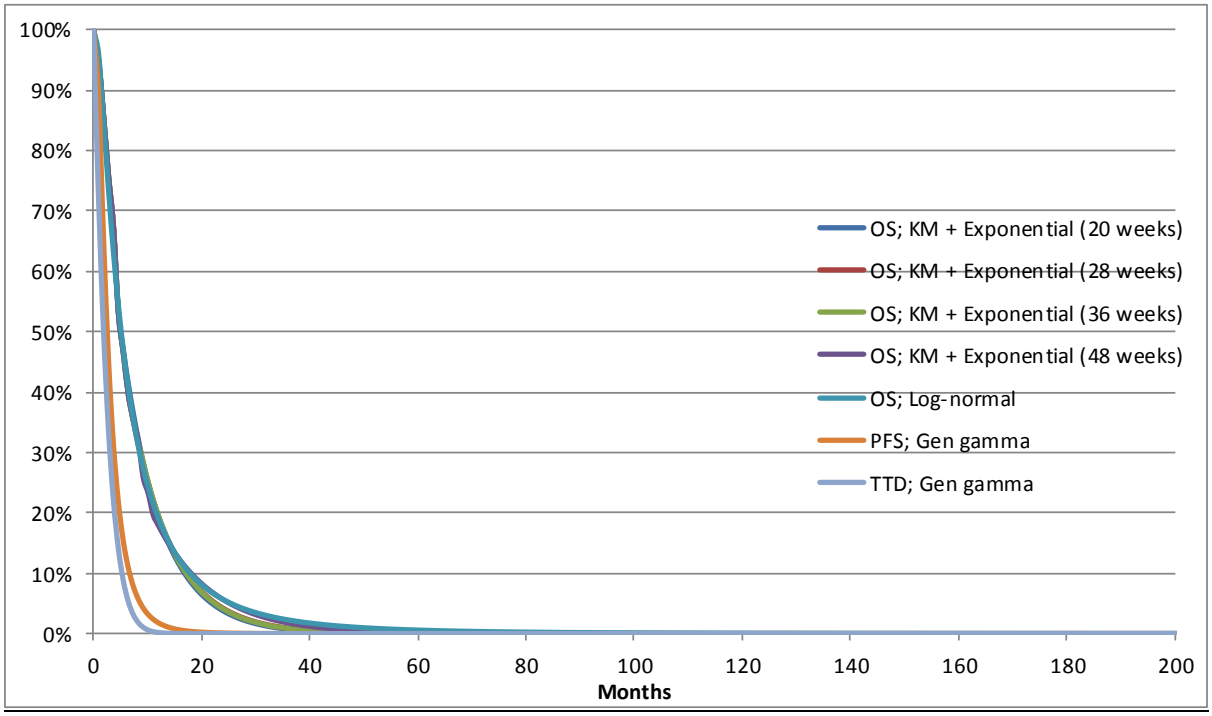
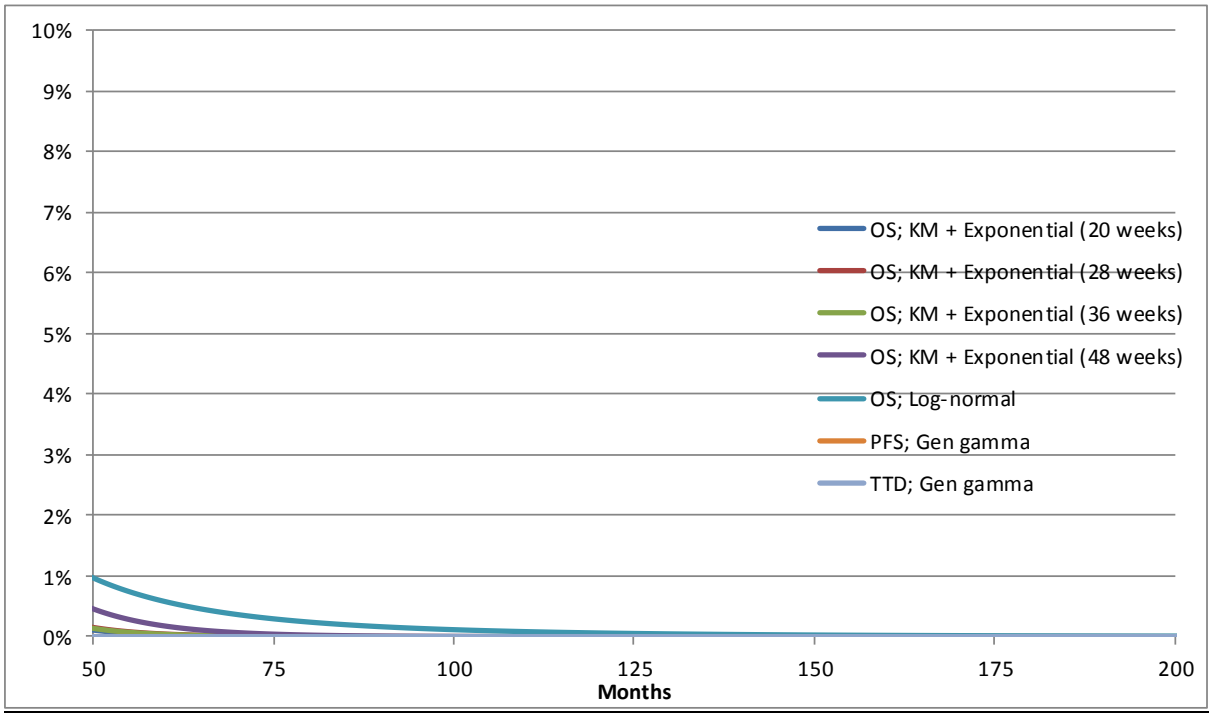


Figure 2: IC OS, PFS and TTD





2. Factual inaccuracy correction by the company

The ERG agrees with the company that the following phrase is factual incorrect:

"In a scenario analysis, the ERG used treatment-independent utilities to account for this uncertainty and for the missing data. This increased the company's ICER range for the scenario without a stopping rule from between £44,000 and £47,000 per quality-adjusted life year (QALY) gained to between £62,000 and £67,000 per QALY gained."

For convenience, the Table from the ERG addendum of February (with the appropriate ICERs) is copied below (slightly modified for clarity). The ICER range of £62,000 and £67,000 from the phrase above is based on scenario 2 of this Table while scenario 1 should have been used (i.e. ICER range of £66,000 and £75,000 per QALY gained).

Additionally, given that no new evidence has been provided, the ERG base-case provided in the Table below is still applicable. However, given the considerations of the different utility models (see section 3), the ERG wishes to highlight the relevance of scenario 2 in Table 1.

Table 1: ERG base-case and requested additional scenario analyses (with PAS for nivolumab) from ERG addendum (February 2017)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
ERG Base-case							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,459	0.67	0.36	[redacted]	0.52	[redacted]	£47,419
Paclitaxel	11,859	0.67	0.36	[redacted]	0.52	[redacted]	£44,007
Methotrexate	11,525	0.67	0.36	[redacted]	0.52	[redacted]	£44,820
Scenario 1: using piecewise approach to predict OS; based Kaplan-Meier curves (first phase) and exponential distribution (second phase) as well as used treatment-independent utilities							
Cut-off point: 20 weeks							
Nivolumab	[redacted]	0.93	[redacted]				
Docetaxel	10,358	0.63	0.34	[redacted]	0.30	[redacted]	£72,037
Paclitaxel	11,758	0.63	0.34	[redacted]	0.30	[redacted]	£66,727
Methotrexate	11,424	0.63	0.34	[redacted]	0.30	[redacted]	£67,993
Cut-off point: 28 weeks							
Nivolumab	[redacted]	0.92	[redacted]				
Docetaxel	10,366	0.63	0.34	[redacted]	0.29	[redacted]	£74,885
Paclitaxel	11,766	0.63	0.34	[redacted]	0.29	[redacted]	£69,355
Methotrexate	11,432	0.63	0.34	[redacted]	0.29	[redacted]	£70,674
Cut-off point: 36 weeks							
Nivolumab	[redacted]	0.94	[redacted]				
Docetaxel	10,365	0.63	0.34	[redacted]	0.31	[redacted]	£71,567
Paclitaxel	11,765	0.63	0.34	[redacted]	0.31	[redacted]	£66,293
Methotrexate	11,431	0.63	0.34	[redacted]	0.31	[redacted]	£67,551
Cut-off point: 48 weeks							
Nivolumab	[redacted]	0.96	[redacted]				
Docetaxel	10,413	0.65	0.35	[redacted]	0.30	[redacted]	£70,849
Paclitaxel	11,813	0.65	0.35	[redacted]	0.30	[redacted]	£65,628
Methotrexate	11,479	0.65	0.35	[redacted]	0.30	[redacted]	£66,872
Scenario 2: using a disutility of [redacted] (difference in post progression utility between nivolumab and IC) for patients that discontinued nivolumab treatment							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,459	0.67	0.36	[redacted]	0.52	[redacted]	£66,560
Paclitaxel	11,859	0.67	0.36	[redacted]	0.52	[redacted]	£61,770
Methotrexate	11,525	0.67	0.36	[redacted]	0.52	[redacted]	£62,912

Source: ERG addendum of February

IC: investigator choice; ICER: incremental cost-effectiveness; QALYs quality adjusted life-years

3. Appendix 1 submitted by the company

In the Appendix the company provided more details on the utility values estimated using the mixed model. Although this is helpful, it is still unclear whether the missing data is dealt with appropriately (assuming that data are missing at random conditional on that the model being specified correctly). Moreover, given the different models, it becomes even more questionable whether it is plausible to extrapolate the relatively high post-progression utility for nivolumab over the entire time horizon (as also stated in the ERG addendum of February 2017). Table 2 provides an overview of the different models fitted by the company. Model 6 is considered 'optimistic' by the company (and used in its base case) whereas Model 7 is considered pessimistic by the company. The ERG however, wonders why the company did not opt to use Model 1 or Model 2, 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. Also, based on Model 1 and Model 2, there might be scope for adding a variable for treatment status to the model. Hence, Scenario 2 from Table 1 (using a disutility of [redacted] (difference in post progression utility between nivolumab and IC) for patients that discontinued nivolumab treatment) might be relevant to consider.

Table 2: Utilities estimated using the mixed model

Coefficients	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IC	[redacted]			[redacted]	[redacted]	[redacted]	
PD	[redacted]	[redacted]				[redacted]	[redacted]
off tx	[redacted]	[redacted]	[redacted]	[redacted]			
IC × PD	[redacted]	[redacted]				[redacted]	
PD × off tx	[redacted]						
IC × off tx	[redacted]			[redacted]			
IC × PD × off tx	[redacted]						
Estimated utilities							
IC PF on tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
off tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD on tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
off tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab PF on tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
off tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD on tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
off tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
difference PF on tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
off tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD on tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
off tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source Appendix 1 of company response to ACD

Abbreviations: PFS, progression free; PD, progressed disease tx, treatment

4. Appendix 2 submitted by the company

Here the company provides its base-case as well as scenarios using the piecewise approach, KM followed by a lognormal curve. All these analyses were performed using the 'optimistic' (Model 6 in Table 2) and pessimistic (Model 7 in Table 2) utilities as termed by the company. In these analyses no diminishing utility or waning treatment over time was incorporated. The 'optimistic' base case (with ICERs ranging between £43,690 and£47,086) is identical to the company's base-case (without clinical stopping rule) that was reported in the submission in February. In these analyses, the company seems to demonstrate that it is not the approach to estimating OS that is pivotal to determining the cost effectiveness of nivolumab versus IC, but rather the approach to estimating utility. It should however be noted that the in the piecewise approach to estimate OS a lognormal curve is used (while exponential is preferred by the committee). Finally, Table 7 (in Appendix 2 submitted by the company) provides an overview of selected analyses that are presented thus far.

References

[1] Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Report by the Decision Support Unit [PDF provided with the company's submission]. Sheffield: School of Health and Related Research (ScHARR), 2011 (updated 2013). 52p.

Table 1: ERG base-case (see original ERG report and addendum submitted February 2017 for more details) with new PAS of [redacted]

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
ERG Base-case							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,459	0.67	0.36	[redacted]	0.52	[redacted]	£42,336
Paclitaxel	11,859	0.67	0.36	[redacted]	0.52	[redacted]	£38,924
Methotrexate	11,525	0.67	0.36	[redacted]	0.52	[redacted]	£39,738
Scenario 1: using piecewise approach to predict OS; based Kaplan-Meier curves (first phase) and exponential distribution (second phase) as well as used treatment-independent utilities							
Cut-off point: 20 weeks							
Nivolumab	[redacted]	0.93	[redacted]				
Docetaxel	10,358	0.63	0.34	[redacted]	0.30	[redacted]	£64,128
Paclitaxel	11,758	0.63	0.34	[redacted]	0.30	[redacted]	£58,819
Methotrexate	11,424	0.63	0.34	[redacted]	0.30	[redacted]	£60,084
Cut-off point: 28 weeks							
Nivolumab	[redacted]	0.92	[redacted]				
Docetaxel	10,366	0.63	0.34	[redacted]	0.29	[redacted]	£66,648
Paclitaxel	11,766	0.63	0.34	[redacted]	0.29	[redacted]	£61,118
Methotrexate	11,432	0.63	0.34	[redacted]	0.29	[redacted]	£62,436
Cut-off point: 36 weeks							
Nivolumab	[redacted]	0.94	[redacted]				
Docetaxel	10,365	0.63	0.34	[redacted]	0.31	[redacted]	£63,712
Paclitaxel	11,765	0.63	0.34	[redacted]	0.31	[redacted]	£58,439
Methotrexate	11,431	0.63	0.34	[redacted]	0.31	[redacted]	£59,696
Cut-off point: 48 weeks							
Nivolumab	[redacted]	0.96	[redacted]				
Docetaxel	10,413	0.65	0.35	[redacted]	0.30	[redacted]	£63,072
Paclitaxel	11,813	0.65	0.35	[redacted]	0.30	[redacted]	£57,850
Methotrexate	11,479	0.65	0.35	[redacted]	0.30	[redacted]	£59,095
Scenario 2: using a disutility of [redacted] (difference in post progression utility between nivolumab and IC) for patients that discontinued nivolumab treatment							
Nivolumab	[redacted]	1.20	[redacted]				
Docetaxel	10,459	0.67	0.36	[redacted]	0.52	[redacted]	£59,426
Paclitaxel	11,859	0.67	0.36	[redacted]	0.52	[redacted]	£54,636
Methotrexate	11,525	0.67	0.36	[redacted]	0.52	[redacted]	£55,778
IC: investigator choice; ICER: incremental cost-effectiveness; QALYs quality adjusted life-years							

BMS Proposal for Recommendation for use in the Cancer Drugs Fund for ID971:

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

Introduction: this document will cover three main topics which are relevant to determining the next steps of this appraisal. Firstly, updated ICERs are provided: based on a revised commercial proposal and using the Appraisal Committee's preferred economic assumptions. Secondly, the clinical case for access in the licensed patient population (that is, not restricted to a biomarker-defined subgroup) will be detailed. Finally, an overview of the data to be collected during the period of access via the CDF and how it will address the Committee's current uncertainty, will be provided.

Revised Commercial Arrangement

BMS understand that the Appraisal Committee have concerns about the cost-effectiveness of nivolumab for use in the full, licensed patient population. Given this uncertainty, BMS are willing to offer a larger confidential commercial discount than previously proposed to ensure that this uncertainty is addressed. The commercial scheme will be administered directly with NHS England as a confidential rebate on the administration of nivolumab for patients with SCCHN after platinum-based chemotherapy. The rebate has been calculated to ensure that all scenarios presented to the Appraisal Committee are under the threshold of £50,000 per QALY gained. Given that a range of plausible ICERs are presented, it should be noted that a number of scenarios are well under the £50,000 threshold for cost-effectiveness under the end of life criteria.

The ICERs for each combination of the scenarios listed below are presented in Table 1, with the revised rebate applied for nivolumab. All other model parameters and assumptions have remained unchanged to those that were previously presented to NICE as part of BMS' response to the Appraisal Consultation Document.

1) The piecewise lognormal distribution for overall survival, implemented at the following cut-points: 20 weeks, 36 weeks and 48 weeks
2) Utility analysis estimated using model 6 and 7 from the mixed regression model, relating to either treatment specific utility values or treatment independent utility values, respectively
3) With a 2-year stopping rule and with treatment as per CheckMate 141 protocol
4) Implementation of a 5-year treatment waning effect is provided in the appendix

Table 1: ICERs for nivolumab versus comparators (with revised rebate for nivolumab)

ICER (£ per QALY) nivolumab versus – *no clinical stopping for nivolumab, as per CheckMate-141 protocol*			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	£34,337	£31,173	£40,075
Paclitaxel	£30,900	£28,078	£36,017
Methotrexate	£31,748	£28,842	£37,019
Treatment-independent utility			
Docetaxel	£43,297	£39,290	£49,999
Paclitaxel	£38,963	£35,390	£44,936
Methotrexate	£40,033	£36,352	£46,186
ICER (£ per QALY) nivolumab versus – *with 2-year clinical stopping rule for nivolumab*[a]			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	£32,016	£29,083	£37,335
Paclitaxel	£28,579	£25,989	£33,277
Methotrexate	£29,427	£26,753	£34,279
Treatment-independent utility			
Docetaxel	£40,371	£36,656	£46,581
Paclitaxel	£36,037	£32,756	£41,518
Methotrexate	£37,107	£33,719	£42,768

[a] Assuming all patients who are still receiving nivolumab at two years stop treatment at two years.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Request for approval in a broad population aligned with the licensed indication

BMS also understand that the Committee wish to maximise clinical benefit for patient by funding the treatments for use in patients who will derive the maximum clinical benefit. However, BMS believe that it would not be appropriate to restrict an approval to a PD-L1 positive subgroups for the following reasons:

- The European Medicines Agency has approved nivolumab for all patients, irrespective of PD-L1 expression, indicating that the risk/benefit profile of the drug has been demonstrated in the entire patient population
- Nivolumab demonstrated a survival benefit in the overall population, regardless of PD-L1 expression level. In patients with PD-L1 < 1%, the Kaplan-Meier OS curves separate after approximately 8 months in favour of nivolumab (HR, 0.89; [95% CI, 0.54-1.45]; P = 0.17)
- In the CM-141 study [redacted] out of 6 complete responses and [redacted] out of 26 partial responses occurred in patients in the PD-L1 <1% group highlight that a lack of PD-L1 does not exclude a response.
- Additionally, subgroup analysis from the CheckMate-141 trial has very clearly shown that patients with HPV positive disease, derived significant benefit. A restriction on the basis of PD-L1 status would deny access to those patients who were HPV

positive, for whom there is very clear benefit.[1] Whilst PD-L1 testing is a necessary starting point, this single marker, analysed at a single point in time, from a single biopsy is unlikely to be useful as a sole marker or determinant of response/toxicity. Given the complexity of the immune system, the number of other potential biomarkers and more importantly, that the immune response is a highly dynamic process, it is more realistic that a panel of markers, yet to be defined, are likely needed.

- The CheckMate-141 trial was not powered to show a difference between the PD-L1 subgroups. The inherent uncertainties around the value of the PD-L1 as a predictive test, allied to the statistical lack of power to detect such differences would make any decisions on restricting the patient population unsafe, and has the very real risk that patients will potentially be denied a beneficial treatment.

Data collection proposal

BMS understand that the main areas of uncertainty for the Appraisal Committee are regarding the clinical benefit seen in the PD-L1 negative patient population, as well as the potential for long-term survival benefit, which we expect because of the mechanism of action of nivolumab.

BMS are proposing that data continues to be collected from its existing ongoing trial programme, namely the CheckMate-141 trial, in anticipation of a review at the end of 2018 or 2019. The CheckMate-141 trial is currently scheduled to reach a minimum of two years of follow-up for all patients with a corresponding database lock in **September 2017**. Further data will be available at that point, though follow-up is still likely to be insufficient to address existing uncertainties regarding the potential for long-term benefit with nivolumab.

BMS is therefore proposing to continue following patients up for survival to support further database locks at subsequent landmark time points. Specifically, an analysis of survival at three years or four years of minimum follow-up would be feasible.

Minimum survival follow-up	Timeline	Status
Two years	September 2017	DBL scheduled
Three years	September 2018	To be scheduled
Four years	September 2019	To be scheduled

It is also possible to provide survival outcomes by PD-L1 status for longer time points, namely three and four years and BMS is willing to provide cost-effectiveness analysis by PD-L1 status, at the time of review, to address the Committee's uncertainty.

The minimum follow-up of four years would be reached in September 2019. BMS wold propose a review to commence no later than this point, though consideration should be given to the required timeframe to fully address the Committee's current uncertainties.

[1] Reference: Ferris et al., Further Evaluations of Nivolumab Versus Investigator's Choice Chemotherapy for Recurrent or Metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (SCCHN): CheckMate-141. ASCO 2016

Appendix 1: ICERs for nivolumab versus comparators (with revised rebate for nivolumab) – with a 5-year treatment waning effect for nivolumab

ICER (£ per QALY) nivolumab versus – *no clinical stopping for nivolumab, as per CheckMate-141 protocol*			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	£35,855	£32,359	£41,784
Paclitaxel	£32,251	£29,135	£37,538
Methotrexate	£33,141	£29,931	£38,586
Treatment-independent utility			
Docetaxel	£45,619	£41,103	£52,548
Paclitaxel	£41,034	£37,007	£47,209
Methotrexate	£42,166	£38,018	£48,527
ICER (£ per QALY) nivolumab versus – *with 2-year clinical stopping rule for nivolumab*[a]			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	£33,421	£30,182	£38,917
Paclitaxel	£29,818	£26,957	£34,671
Methotrexate	£30,707	£27,753	£35,719
Treatment-independent utility			
Docetaxel	£42,523	£38,337	£48,943
Paclitaxel	£37,938	£34,241	£43,603
Methotrexate	£39,070	£35,252	£44,921

[a] Assuming all patients who are still receiving nivolumab at two years stop treatment at two years.

Waning of efficacy was implemented in the model by increasing the time-dependent hazard rate of death with nivolumab to a hazard rate that was the same as the control arm (i.e., the relative hazard rate was set to one for nivolumab versus investigator's choice), for all remaining cycles after the specified time point.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

BMS Proposal for Recommendation for use in the Cancer Drugs Fund for ID971:

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

Additional evidence from the PD-L1 <1% and ≥1% subgroups

Dear Helen,

Thank you for letter dated 7th July. In response to your information request, please find provided below the cost-effectiveness results for the following populations:

- Overall population (n=361)
- PD-L1 expression ≥1% (n=149)
- PD-L1 expression <1% (n=111)

Analyses have been conducted using the Committee's preferred assumptions:

- The piecewise model using the log-normal distribution to model overall survival – extrapolated from 20, 36 and 48 weeks
- Treatment benefit with nivolumab stopped at 5 years
- No treatment stopping rule for nivolumab
- Using both treatment-dependent and treatment-independent utility values (model 6 and model 7)
- Using the ERG's amendments to the company's 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 investigator's choice arms from the latest database lock of CheckMate 141).

BMS would like to formally note that it does not agree with the arbitrary stopping of treatment benefit for nivolumab at five years and highlights that this does not match with the clinical evidence present in other indications. Additionally, the lack of incorporation of a two-year treatment stopping rule should preclude its implementation as part of commissioning policy in the interests of consistency.

Analyses are presented using the following price scenarios for nivolumab:

- The proposed CDF price (***only applicable for an all-comers recommendation in the CDF only***)
- [redacted]% PAS – the current baseline commissioning discount, as per the original Company Evidence Submission)

Please note that cost-effectiveness results for the price that was presented in May's committee meeting have not been presented here. This Patient Access Scheme was proposed contingent on a recommendation in baseline commissioning for the *full* licensed patient population. As indicated by the letter received from NICE, this is not a potential outcome for this appraisal, as this time.

Additionally, ICERs for both the PD-L1 ≥1% and PD-L1<1% subgroups have been marked as commercial in confidence - BMS is providing these cost-effectiveness analyses contingent on their confidentiality.

Addressing the committee uncertainty

BMS highlighted the current limitations associated with a restricted approval based on a PD-L1 subgroup in our original proposal for use in the CDF. The Committee would however like to understand the potential cost-effectiveness in these subgroups to understand whether further data collection in the CDF could address the uncertainty in the entire patient population.

By implementing all the Committee's preferred assumptions, including an arbitrary restriction on duration of treatment benefit, nivolumab is shown to be plausibly cost-effective across all populations, including low expressors. The use of different cut-points however leads to a range of plausible ICERs. This indicates a clear rationale for further data collection for all patients via the CDF, to address this uncertainty. The clinical implausibility of certain cut-points (namely 36 weeks) must be considered when interpreting the meaning of these results.

Table 1: Overall population (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	£36,101	£32,564	£42,110
Paclitaxel	£32,480	£29,325	£37,839
Methotrexate	£33,442	£30,186	£38,974
Treatment-independent utility			
Docetaxel	£45,996	£41,413	£53,040
Paclitaxel	£41,382	£37,294	£47,660
Methotrexate	£42,608	£38,388	£49,089

Table 2: Overall population (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	£49,960	£44,957	£58,451
Paclitaxel	£46,338	£41,718	£54,180
Methotrexate	£47,300	£42,579	£55,315
Treatment-independent utility			
Docetaxel	£63,653	£57,174	£73,622
Paclitaxel	£59,038	£53,055	£68,243
Methotrexate	£60,264	£54,149	£69,672

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 3: PD-L1 ≥1% subgroup (with [redacted]% discount to nivolumab) [*Not applicable*]

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]

Table 4: PD-L1 ≥1% subgroup (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

Table 5: PD-L1 <1% subgroup (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]

Table 6: PD-L1 <1% subgroup (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

36 week cut-off point

The 36-week analysis is producing results which are inconsistent with those produced by either the 20 week or 48 week cut-point. These cut points were not selected based on their appropriateness for the PD-L1≥1 or PD-L1<1% data but based on the clinical data for the Intention-to-Treat population. As such, these cut-points may not be relevant for these patient subgroups and/or lead to logical inconsistencies.

The 36-week extrapolation creates a kink in the shape of the overall survival curve for the investigator's choice (IC) arm, possibly due to the small patient numbers in this subgroup at this time point. The IC curve crosses the nivolumab curve and plateaus estimating 10% of patients alive at 3 years. The resulting survival curve is therefore wholly clinically implausible given the known prognosis for patients with recurrent/metastatic squamous cell head and neck cancer after platinum therapy, and

inconsistent with clinical advice provided as part of this appraisal. BMS therefore propose that this cut-point is not relevant for decision-making.

Figure 1: Overall survival: 36-week cut-off with lognormal extrapolation (PD-L1<1%)

Additional survival modelling analysis

BMS have also provided the cost-effectiveness analysis for all three patient populations using the BMS preferred overall survival modelling assumptions: the fully parametric lognormal model. This further demonstrates that all subgroups are cost-effective at the proposed CDF commercial access scheme price and are *plausibly* cost-effective with the current baseline commissioning PAS. BMS are proposing that access via the CDF with the collection of longer-term trial data can address the current uncertainty presented by the use of different survival extrapolations.

Table 7: Lognormal – fully parametric (with [redacted]% discount to nivolumab)

Population	Overall	PD-L1 ≥1%	PD-L1 <1%
Treatment-specific utility			
Docetaxel	£34,315	[redacted]	[redacted]
Paclitaxel	£30,903	[redacted]	[redacted]
Methotrexate	£31,809	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	£41,538	[redacted]	[redacted]
Paclitaxel	£37,407	[redacted]	[redacted]
Methotrexate	£38,505	[redacted]	[redacted]

Table 8: Lognormal – fully parametric (with [redacted]% discount to nivolumab)

Population	Overall	PD-L1 ≥1%	PD-L1 <1%
Treatment-specific utility			
Docetaxel	£47,372	[redacted]	[redacted]
Paclitaxel	£43,959	[redacted]	[redacted]
Methotrexate	£44,866	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	£57,343	[redacted]	[redacted]
Paclitaxel	£53,212	[redacted]	[redacted]
Methotrexate	£54,309	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NE: non-evaluable; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

Conclusion

BMS have further addressed the Committee's uncertainty by presenting the cost-effectiveness results for all-comers and PD-L1 positive and negative patients, using all of the Committee's preferred modelling assumptions.

These preferred assumptions include an arbitrary restriction on duration of treatment benefit with nivolumab but without any treatment stopping rule, both of which provide a conservative assessment of the cost-effectiveness of nivolumab.

The results show however, there is a strong rationale for making nivolumab available for all-comers via the CDF; with both a plausible potential for satisfying the criteria for routine use and a plan for collecting further data to address the existing uncertainty, namely the long-term survival extrapolation.

Finally, BMS have proposed a commercial arrangement to allow access for all-comers in the CDF, but would like to highlight that this commercial arrangement has been designed given the cost-effectiveness case for all-comers only (i.e. not based on a PD-L1 restriction) and so should be considered for the all-comers population only.

Appendix

Additional evidence from the PD-L1 <1% and ≥1% subgroups: with 2-year stopping rule applied for nivolumab

Cost-effectiveness results are provided below for the following populations:

- Overall population (n=361)
- PD-L1 expression ≥1% (n=149)
- PD-L1 expression <1% (n=111)

Analyses have been conducted using the Committee's preferred assumptions:

- The piecewise model using the log-normal distribution to model overall survival – extrapolated from 20, 36 and 48 weeks (and using the fully parametric lognormal distribution to model overall survival)
- Treatment benefit with nivolumab stopped at 5 years
- Using both treatment-dependent and treatment-independent utility values (model 6 and model 7)
- Using the ERG's amendments to the company's 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 investigator's choice arms from the latest database lock of CheckMate 141).

And with a 2-year stopping rule applied for nivolumab treatment (100% of those patients receiving nivolumab at two years are modelled to stop treatment at two years)

Analyses are presented using the following price scenarios for nivolumab:

- The proposed CDF price (***only applicable for an all-comers recommendation in the CDF***)
- The Patient Access Scheme price that was submitted as part of the original Company Evidence Submission ([redacted]%)

Table 1: Overall population (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	£33,656	£30,377	£39,226
Paclitaxel	£30,034	£27,138	£34,955
Methotrexate	£30,996	£27,999	£36,090
Treatment-independent utility			
Docetaxel	£42,881	£38,632	£49,408
Paclitaxel	£38,266	£34,513	£44,028
Methotrexate	£39,492	£35,607	£45,457

Table 2: Overall population (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	£46,598	£41,951	£54,488
Paclitaxel	£42,977	£38,712	£50,217
Methotrexate	£43,939	£39,573	£51,352
Treatment-independent utility			
Docetaxel	£59,370	£53,352	£68,630
Paclitaxel	£54,756	£49,232	£63,251
Methotrexate	£55,982	£50,327	£64,680

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table 3: PD-L1 ≥1% subgroup (with [redacted]% discount to nivolumab) [*Not applicable*]

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]

Table 4: PD-L1 ≥1% subgroup (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

Table 5: PD-L1 <1% subgroup (with [redacted]% discount to nivolumab) [*Not applicable*]

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]

Table 6: PD-L1 <1% subgroup (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Piecewise lognormal cut-off point:	**20 weeks**	**36 weeks**	**48 weeks**
Treatment-specific utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

Table 7: Fully parametric lognormal (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Population:	**Overall**	**PD-L1 ≥1% [*Not applicable*]**	**PD-L1 <1% [*Not applicable*]**
Treatment-specific utility			
Docetaxel	£32,011	[redacted]	[redacted]
Paclitaxel	£28,599	[redacted]	[redacted]
Methotrexate	£29,505	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	£38,749	[redacted]	[redacted]
Paclitaxel	£34,618	[redacted]	[redacted]
Methotrexate	£35,716	[redacted]	[redacted]

Table 8: Fully parametric lognormal (with [redacted]% discount to nivolumab)

ICER (£ per QALY) nivolumab versus			
Population:	**Overall**	**PD-L1 ≥1%**	**PD-L1 <1%**
Treatment-specific utility			
Docetaxel	£44,205	[redacted]	[redacted]
Paclitaxel	£40,793	[redacted]	[redacted]
Methotrexate	£41,699	[redacted]	[redacted]
Treatment-independent utility			
Docetaxel	£53,509	[redacted]	[redacted]
Paclitaxel	£49,379	[redacted]	[redacted]
Methotrexate	£50,476	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy: critique on BMS submission of August 2017

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

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Declared competing interests of the authors
None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Nigel Armstrong acted as project lead as well as systematic reviewer and health economist on this assessment, critiqued the clinical effectiveness methods and evidence as well as the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Xavier Pouwels, Remziye Zaim and Ching-Yun Wei acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Robert Wolff and Rob Riemsma acted as systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore and Maiwenn Al acted as health economists on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Reproducibility of PD-L1 <1% and ≥1% subgroups results presented by BMS

Based on the updated economic models received from the company, the ERG was able to reproduce the PD-L1 <1% and ≥1% subgroups results submitted by the company performed using the following assumptions (Tables 3-6 in document: "ID971 BMS Response to nivolumab letter PD-L1 14072017KM [ACIC].docx"):

- The piecewise model using the log-normal distribution to model overall survival – extrapolated from 20, 36 and 48 weeks
- Treatment benefit with nivolumab stopped at 5 years
- No treatment stopping rule for nivolumab
- Using both treatment-dependent and treatment-independent utility values (model 6 and model 7)
- Using the ERG's amendments to the company's model (adding the cost and disutility for pneumonitis and using treatment-independent proportions for subsequent treatments)

Validity of PD-L1 <1% and ≥1% subgroups results presented by BMS

The company initially submitted the results of the PD-L1 subgroup analyses only. After the ERG requested more details, the company provided the economic models. However, this was not supplemented by details on the technical implementation of these subgroups in the economic model nor the accompanying justifications. Given the lack of details as to how the subgroup results were obtained, the ERG is unable to assess the validity of the PD-L1 <1% and ≥1% subgroups results. For instance it is unclear what is exactly changed in the model to incorporate the subgroups and although "BMS have confirmed that no other changes were made to the model apart from those mentioned in the additional evidence submission" unexpected adjustments to the economic model were identified by the ERG (e.g. columns AJ and AK in the nivolumab, docetaxel, methotrexate and paclitaxel traces sheets). Moreover, it is unclear whether the choices for parametric curves (e.g. for progression free survival and time to treatment discontinuation) are plausible / justifiable for the PD-L1 subgroups. Currently, for progression free survival and time to treatment discontinuation, the same parametric distributions are used for the PD-L1 subgroups as for the total population, but there is no reason to believe that these distributions will provide the best fit for the subgroup data.

From: [redacted]
Sent: 24 August 2017 17:18
To: TA Comm D <TACommD@nice.org.uk>; Helen Knight <Helen.Knight@nice.org.uk>; Nwamaka Umeweni <Nwamaka.Umeweni@nice.org.uk>
Cc: [redacted]
Subject: RE: Important - query: nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

Dear Helen and team,

RE: Important - query: nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy [ID971]

Thank you for your email. Please find below (in blue) the responses to the questions you posed in your email this morning. BMS would also like to share with you our thoughts on this appraisal and the discussion to date, especially in light of the recent conversations and Committee meeting regarding nivolumab for NSCLC (ID811 and ID900).

If you have any further, or follow-up queries, then please do not hesitate to contact me.

Best wishes

[redacted]

Please can you confirm that the EPAR contains the most recent clinical data (PFS and overall survival), in particular KM plots and Forrest plots for Checkmate-141 by the different populations; all-comers, and by level of PD-L1 expression? It is noted that the most recent database lock in the EPAR is 20 September 2016.

Yes, BMS can confirm that the data included in the EPAR is from the most recent data cut available.

Please note the updated analysis by PD-L1 expression (<1% and ≥1%) shows an improvement in the hazard ratio for both expressing and non-expressing patients, compared to the hazards ratios from the primary data base lock. In subjects with < 1% PD-L1 expression, the OS Kaplan-Meier curves initially overlapped, and then separated after approximately 4 months in favour of nivolumab.

We have previously received KM plots from the original database lock according to the different patient sub-populations (in your original submission). We also received updated KM plots from the latest database lock (dated 20 September 2016) in response to the ACD. However, this was only for the all-randomised population and not by PD-L1 expression; therefore we want to check the information in the EPAR is the most recent data available for all of the groups. Yes, that is correct.

2) Please can you also confirm that, in you economic analyses according to PD-L1 expression, you have used the most up to date clinical data, and confirm this is from the 20 September 2016 database lock.

Similarly, we can confirm that the data included in the economic model is from the most recent data cut available [20th September 2016].

3) Finally, the EPAR includes KM plots for several PD-L1 expression according to other characteristics, for example, tumour-associated immune cells TAICs. Please can BMS comment on the relevance of these data?

Growing evidence suggests that biomarkers beyond, or in addition to, PD-L1 may be associated with clinical benefit to checkpoint inhibition. Tumour-associated immune cells can also express PD-L1. Since immune cells are capable of infiltrating the tumour microenvironment, the presence and location of PD-L1 positive immune cells and its association with clinical outcomes to anti-PD-1/anti-PD-L1 treatment is an area of interest. As a result, the EMA requested BMS to conduct this additional, post-hoc analysis on the baseline samples available from the CheckMate-141 trial.
This exploratory post-hoc analysis evaluated the association of tumour PD-L1 expression and PD-L1 positive expression on tumour-associated immune cells (TAICs), and whether these variables could be of predictive value to nivolumab treatment in SCCHN.
It is important to note that PD-L1 positive TAIC assessment performed in this hypothesis-generating analysis in the tumour PD-L1 expression subgroups is 1) descriptive, 2) not sufficiently powered, and 3) based on qualitative data collected using an assay that has not been validated for assessing TAICs.

These preliminary findings suggest that PD-L1 positive TAICs may play a role in identifying recurrent or metastatic SCCHN patients who are more likely to respond to nivolumab therapy in patients with < 1% tumour cell PD-L1 expression. These data are interesting preliminary results that support further investigation. However, TAIC PD-L1 analyses are premature to implement in clinical practice until clinical utility is established, low inter-reader reliability is addressed, and a validated, and an approved diagnostic is available.

An analysis of outcomes by PD-L1 and HPV-status (determined by p16 immunohistochemistry [IHC]) was conducted because of the clinically relevant role HPV plays in outcomes for patients with oropharyngeal cancer.

Kind regards,

[redacted]

[redacted]

BMS position on ID971: nivolumab for SCCHN

A number of parallel's have been drawn between the SCCHN and NSCLC appraisals by NICE and the NHS. However, there are significant and meaningful differences which should be considered as part of this appraisal.

- Squamous cell carcinoma of the head and neck is, as the name implies, histologically similar to squamous NSCLC, **not** non-squamous NSCLC. We would request the committee adopt a similar consideration to that of the squamous cell NSCLC appraisal
- Data from the CheckMate-141 study demonstrated OS benefit with nivolumab versus investigator choice, regardless of PD-L1 expression based on PD-L1 scoring only on tumour cells
    - Numerically the benefit was greater in the ≥1% tumour PD-L1 expression subgroup relative to the < 1% tumour PD-L1 expression subgroup however the trial was not powered to identify statistically significant differences
    - Importantly, 2 out of 6 complete responses and 6 out of 27 partial responses occurred in a PD-L1<1% group
    - The current commercial offer addresses this uncertainty and is only available for all-comers and not for a patient sub-group
- Limiting the recommendation to simply PD-L1–expressing tumour cells neglects other immune factors (type and degree of immune cells present) and other key influences (e.g. HPV status, mutational type and load), that might be equally important to predicting responses to anti–PD-1/PD-L1 therapies
    - E.g. the hazard ratio for PD-L1<1 and HPV-positive patients is 0.55 (0.25, 1.22)
- At this time, UK clinical experts are not in favour of selecting patients in their clinical practice via a single PD-L1 testing result
    - BMS and clinicians only want to measure PD-L1 for the purposes of research and adding to our knowledge base
- No routine testing for PD-L1 occurs in the UK for SCCHN. The incidence is therefore difficult to determine. Data from clinical practice in the US indicates rates of expression around [redacted] compared to study CheckMate-141 (57.3%). The all-comers ICER may therefore be conservative compared to the true ICER in UK practice
    - On this basis, recalculating the plausible ICER gives a value between £[redacted]-£[redacted] (nivolumab vs. docetaxel) using the 20 or 48 week cut points respectively, and treatment independent utility values
- The potential budget impact [if all 576 eligible patients were treated] of this indication [redacted], based on an 'all-comers' recommendation at the proposed CDF price, compared to a PD-L1 restriction at the current approved PAS

Average per patient drug cost		Budget impact	
		Trial based estimate of PD-L1≥1 proportion (57.3%)	PD-L1≥1 proportion based on expression observed in other countries ([redacted]%)
PD-L1≥1% @ [redacted]% discount	[redacted]	[redacted]	[redacted]
All-comers @ [redacted]% discount ([redacted])	[redacted]	[redacted]	[redacted]