NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

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

2. **Appraisal Consultation Document (ACD)** as issued to consultees and commentators

3. **Comments on the Appraisal Consultation Document from Bristol-Myers Squibb:**
   a. Main response
   b. Appendix
   c. Appendix 2

4. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Head and Neck Cancer UK

5. **Comments on the Appraisal Consultation Document from experts:**
   a. Dr Andrew Sykes – clinical expert, nominated by Bristol-Myers Squibb

There were no comments on the appraisal consultation document received through the NICE website.

6. **Evidence Review Group critique of company comments on the ACD**
   a. Main critique
   b. Revised base case results

7. **Further ACD response from Bristol-Myers Squibb including updated PAS**

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

Nivolumab for treating recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy [ID1585]

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 Social Care 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 document (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 and Social Care, 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.		Bristol Myers Squibb Pharmaceuticals Ltd	Bristol-Myers Squibb (BMS) Pharmaceuticals Limited would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for nivolumab for treating recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) after platinum-based chemotherapy [ID1585] (CDF Review of TA490). We are highly disappointed that the Appraisal Committee has ignored the clinical expert feedback 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. The unmet need in these patients has been heightened during the ongoing COVID-19 pandemic: in the UK between March and May 2020, urgent referrals for people with a suspicion of head and neck cancer dropped by 59%, which is projected to significantly impact 5-year survival time in these patients.[1] We believe that the basis for this preliminary decision relies on the Committee reaching several conclusions directly in contradiction to those reached in the original appraisal (TA490) despite the data informing these issues remaining unchanged. In response to the ACD, BMS have presented a revised economic base case to address the Committee's concerns regarding the suitability of implementing a 2-year stopping rule for nivolumab treatment. This revised base case is associated with an incremental cost-effectiveness ratio (ICER) below the willingness-to-pay threshold of £50,000 for medicines which reach the end-of-life criteria and thus demonstrates nivolumab to be a cost-effective use of NHS resources. 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 R/M SCCHN after platinum-based chemotherapy in UK clinical practice.	Comment noted. The views of clinical experts and patient/carer representatives, and the updated economic evidence provided by BMS, were considered by the Appraisal Committee when formulating its recommendations.
2.		Bristol Myers Squibb Pharmaceuticals Ltd	**Section 3.2 (page 6):** The Committee note that "*both [cetuximab combination therapy and pembrolizumab monotherapy] are used earlier in the treatment pathway than nivolumab*" and that *"pembrolizumab is recommended for untreated metastatic or unresectable recurrent SCCHN in adults whose tumours express PD-L1 with a combined positive score of 1 or more. But in NHS clinical practice, people would only have immunotherapy once during the treatment pathway. Therefore, the committee agreed that most people who will be eligible for immunotherapy in later lines of treatment will have tumours that have a PD-L1 score of less than 1."* Similar arguments are reported in Section 3.5 (page 9). The Committee have mis-represented the target population for this submission in the ACD. The Company maintain that there remains an unmet need in the indication of relevance for this submission for patients irrespective of	Comment noted. The committee considered the population in which nivolumab would be used in NHS clinical practice. The committee considered that it is likely most people

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			programmed death ligand 1 (PD-L1) status. The indication of relevance for this submission is: "*nivolumab monotherapy for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) in adults progressing on or after platinum-based therapy*". As shown in Figure 1, this population includes patients who progress following platinum-based therapy in the recurrent or metastatic (R/M) setting and patients who progress following platinum-based therapy as part of an earlier-stage intervention for the treatment of locally advanced disease. Cetuximab in combination with platinum-based chemotherapy is recommended for treating recurrent or metastatic squamous cell cancer of the head and neck in cancers that started in the oral cavity, and pembrolizumab is recommended for untreated metastatic or unresectable recurrent SCCHN for patients whose tumours express PD-L1 with a combined positive score (CPS) of 1 or more (as shown in Figure 1).[2, 3] As patients who have progressed following platinum-based therapy in the locally-advanced setting would be eligible for nivolumab first line in the R/M setting, the conclusion of the Committee that cetuximab and pembrolizumab are used earlier in the treatment pathway than nivolumab is incorrect, with all three eligible for first-line use in the R/M setting for some patients. The Company agree that patients who receive pembrolizumab in the R/M setting would not receive nivolumab in a later line of treatment. However, nivolumab is available to patients who have progressed within 6 months of receiving platinum-based therapy in the locally advanced disease setting. For these patients, there may be a choice between receiving pembrolizumab in those who have PD-L1 >1%, cetuximab in those whose disease began in the oral cavity, or nivolumab in patients regardless of their PD-L1 status or disease origin location. Patients that progressed within 6 months of receiving platinum-based therapy in the locally advanced disease setting constitute a considerable proportion of patients eligible for nivolumab in clinical practice, with a clinical expert consulted as part of this response estimating this proportion to be 40% of patients. Nivolumab would also remain the only immunotherapy option for patients who are PD-L1 <1%, or whose PD-L1 status cannot be determined. This includes patients for whom immediate treatment initiation is clinically necessary and thus PD-L1 status would not be ascertained prior to treatment commencement. In addition to the acknowledgement by the clinical expert in the ACD that the availability of PD-L1 testing varies across the NHS in England (Section 3.5, page 9), a clinical expert consulted as part of this response highlighted that obtaining the results of a PD-L1 test is highly variable between multidisciplinary teams and may take several weeks in UK clinical practice. Therefore, the Company consider nivolumab would address a significant area of unmet need in UK clinical practice despite the introduction of cetuximab and pembrolizumab and regardless of PD-L1 status. **Figure 1: Clinical care pathway for adults with R/M SCCHN who have progressed after platinum-based therapy**	who would receive nivolumab would have tumours with PD-L1 that is less than 1 or indeterminate. Please see FAD sections 3.2 and 3.5.

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			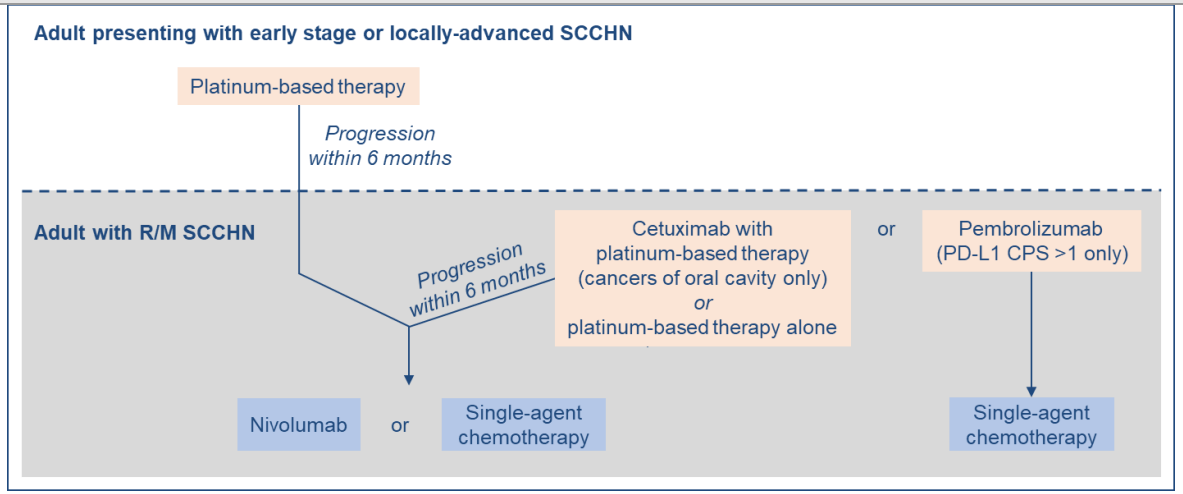 Patients with SCCHN may receive platinum-based therapy first-line in the R/M setting or as part of an earlier-stage intervention for the treatment of locally advanced disease. In the R/M setting, patients with a combined positive score of 1 or more may receive pembrolizumab first-line and patients with cancer of the oral cavity may receive cetuximab. Patients who may be considered eligible for treatment with nivolumab under the anticipated indication for SCCHN are expected to have progressed within 6 months of having received platinum-based therapy, but may have received this therapy in either setting. **Abbreviations:** CPS: combined positive score; R/M: recurrent or metastatic; SCCHN: squamous cell carcinoma of the head and neck.	
3.		Bristol Myers Squibb Pharmaceuticals Ltd	**Section 3.3. (page 8):** The Committee *"concluded that the [intended for] docetaxel subgroup was the most appropriate data source for this guidance review because it was most relevant to NHS clinical practice"* The all-randomised population from the CheckMate 141 trial is the most appropriate data source for this appraisal and is consistent with the decisions made during the original appraisal. The Company appreciate the Committee's acknowledgement that the CheckMate 141 trial was not powered to detect differences between nivolumab and the individual therapies comprising Investigator's Choice (IC), and thus that the comparison versus docetaxel alone lacks the robustness of using the all-randomised population. Therefore, the Company are disappointed that the Committee consider the intended for docetaxel subgroup to be the most appropriate data source for this guidance review, which is inconsistent with the clinical feedback received during the Committee meeting and contrary to the NICE Technical Team's initial conclusion. Furthermore, this was not an area of uncertainty identified as to be resolved within the CDF Exit process given that the Committee in the original appraisal (TA490) found the results of the CheckMate 141 trial to be relevant to the UK population (Final Appraisal Document [FAD], Section 3.8) and concluded that the model structure, where data from the IC arm were used to inform OS, PFS and TTD for docetaxel, methotrexate and paclitaxel, was appropriate for its decision-making (FAD, Section 3.10). The Company are therefore particularly disappointed that the Committee have come to a different conclusion despite no change in the available data.[4] This decision is perverse. As per the Company response to Technical Engagement, in both the all-randomised population and the intended for	Comment noted. The committee concluded that the most appropriate data source for this review is the intention-to-treat population, but the docetaxel subgroup analysis should also be considered. The FAD has been amended to reflect this - please see FAD section 3.3.

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			docetaxel subgroup, nivolumab was associated with a [redacted], indicated by a [redacted]. However, use of the intended for docetaxel subgroup results in a more conservative estimate of the relative treatment effect for nivolumab. Given the smaller sample size of the intended for docetaxel subgroup, the 95% confidence intervals (CIs) associated with the HR are wider than for the all-randomised population. There is considerable overlap in the 95% CIs of the HRs for the all-randomised population and intended for docetaxel subgroup, which means there is not sufficient evidence to advocate a statistically significant difference between these populations in terms of the treatment effect for OS. These results demonstrate that relative treatment effect in the all-randomised population and intended for docetaxel subgroup can be considered similar, and therefore it is more appropriate to use the all-randomised population. The Company note that patient selection and patterns of therapy choice are likely to affect the apparent relative performance of the individual IC agents in the CheckMate 141 trial. Therefore, analysis of treatment efficacy based on the choice of IC will lead to inherent differences in the studied populations. For example, a higher proportion of patients in the docetaxel arm of the intended for docetaxel subgroup had a baseline ECOG score of 0 than patients in the IC arm of the all-randomised population ([redacted]% versus 19.0%) (see Table 5 of the Company's Technical Engagement Response). Conversely, a lower proportion of patients in the nivolumab arm of the intended for docetaxel subgroup had a baseline ECOG score of 0 than patients in the nivolumab arm of the all-randomised population ([redacted]% versus 20.4%). As compared with the all-randomised population, in which the baseline characteristics across treatment arms are more similar, these differences in the intended for docetaxel subgroup may bias the treatment effect in favour of docetaxel. Furthermore, as discussed later in Comment 4, a higher proportion of patients in the docetaxel arm of the intended for docetaxel subgroup received nivolumab or pembrolizumab as a subsequent therapy as compared with the IC arm as a whole (see Table 2). These differences result in further uncertainty in the outcomes observed in the intended for docetaxel subgroup The Company welcome the Committee's acknowledgement that outcomes in clinical practice (as shown by the Systemic Anti-Cancer Therapy [SACT] data) are reflective of what was seen in the clinical trial for nivolumab. It is important to note that the outcomes for nivolumab in the SACT cohort are more similar to the outcomes for the all-randomised population of CheckMate141 than the intended for docetaxel subgroup, as shown in Figure 2, where the Kaplan-Meier (KM) curve for the intended for docetaxel subgroup diverges from the all-randomised and SACT KM plots at approximately nine months. Therefore, the all-randomised population is more reflective of the patients eligible for nivolumab in NHS practice, which is in agreement with the feedback from the clinical expert consulted in the Company response to Technical Engagement. For the reasons outlined above, it is more appropriate to use the all-randomised population for this appraisal, as it is adequately powered to detect differences between treatment arms and is most reflective of patients in this indication. **Figure 2: Kaplan-Meier plots of overall survival in patients receiving nivolumab in the all-randomised population in CheckMate 141, the intended for docetaxel population of CheckMate 141 and in the SACT cohort**	

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			 **Abbreviations:** SACT: Systemic Anti-Cancer Therapy.	
4.		Bristol Myers Squibb Pharmaceuticals Ltd	**Section 3.3 (page 8):** the Cancer Drugs Fund Clinical Lead stated that "*people in the trial (who had an Eastern Cooperative Oncology Group performance status of 0 or 1) would have been fit enough to get docetaxel in NHS clinical practice, and therefore the investigator-choice arm would not be a relevant comparator*." Over the course of this appraisal, the Company have learnt from patients treated with nivolumab within the SACT cohort that the population eligible for nivolumab in clinical practice is broader than those who would otherwise receive docetaxel. As discussed in the Company submission, the SACT cohort included 33 (7%) patients with ECOG performance status 2–3, and 65 (13%) patients with missing ECOG status, a population more in line with the European Medicines Agency (EMA) licence in this indication, which does not exclude based on performance status, than the CheckMate 141 trial. The clinical expert during the appraisal meeting confirmed that treatment with docetaxel is not considered to confer a survival benefit, and is reserved for symptomatic treatment of patients where the benefits may out-weigh the risks of toxicity. This is in alignment with the clinical feedback noted in the Company response to Technical Engagement that the majority of patients in UK clinical practice in this line of therapy would not receive docetaxel, and instead would receive no active treatment at all (i.e. palliative or best supportive care [BSC]); in many cases, this includes patients who are deemed to be clinically "fit enough" to receive docetaxel. As such,	Comment noted. The committee concluded that docetaxel is the most appropriate comparator. Please see FAD section 3. 2. Best supportive care was not identified as a comparator in the original scope.

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<tr><td></td><td></td><td></td><td>clinical expertise indicates that sufficient fitness does not necessarily mean that docetaxel would be received by these patients in the real-world setting. The Company are disappointed that this input provided during the appraisal from the clinical expert, who routinely treats patients with head and neck cancer in UK clinical practice, was dismissed by the Committee in favour of opinion of the Cancer Drugs Fund clinical lead without rationale.
Therefore, while docetaxel represents the most relevant active comparator for nivolumab, the Company maintain that BSC remains a relevant comparator to this appraisal.
Whilst the arguments outlined above for the relevance of the all-randomised population to inform the comparison of nivolumab versus docetaxel still stand, costs may be overestimated for the patient group as a whole if a large proportion of patients who are “fit enough” to receive docetaxel do not in fact receive it in clinical practice. As such, a scenario has been explored using the efficacy data from the all-randomised population where the acquisition and administration costs for docetaxel have been set to £0 (see Table 1); this results in only marginal increases in the ICER which remains below the willingness-to-pay threshold of £50,000, demonstrating the robustness of the ICER estimates and indicating that nivolumab is a cost-effective use of NHS resources.
Table 1: Cost-effectiveness results for the scenario analysis in which docetaxel acquisition and administration costs are set to zero in the all-randomised population using the full model (Model 1) utility
<table>
<tr><th>Assumption</th><th>ICER versus docetaxel (£/QALY gained)</th></tr>
<tr><td>Revised Company base case</td><td>43,207</td></tr>
<tr><td>No docetaxel acquisition and administration costs</td><td>44,597</td></tr>
</table>
Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9. Full details of the revised Company base case are presented in Error! Reference source not found..
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.</td><td></td></tr>
<tr><td>5.</td><td></td><td>Bristol Myers Squibb Pharmaceuticals Ltd</td><td>Section 3.4 (page 8): The ACD states: “The Cancer Drugs Fund Clinical Lead referred to an amendment update of the clinical protocol for CheckMate 141, which meant that people in the investigator-choice arm could have had nivolumab in the extension phase of the trial. The company did not provide data on how many people switched from investigator choice to nivolumab. It is therefore unclear how a treatment switch would have affected overall survival, which could potentially bias the results against nivolumab.”
The Company welcomes the acknowledgement by the Committee that the use of subsequent treatments or crossover in the IC arm could bias the results against nivolumab, and that use of these data without adjustment could represent a conservative approach.
As presented in Table 2, only [redacted] patients crossed over from the IC arm to nivolumab treatment as of the latest data cut of the CheckMate 141 trial (15th October 2019). However, all of these patients had received docetaxel, which may result in greater uncertainty in the survival estimates for the intended for docetaxel subgroup relative to the all-randomised population. In addition, several patients in both the all-randomised population and intended for docetaxel subgroup went on to receive subsequent immunotherapy, with a higher proportion of patients in the docetaxel arm of the intended for docetaxel subgroup receiving subsequent nivolumab ([redacted]% versus [redacted]%) and pembrolizumab ([redacted]% versus [redacted]%) compared with the IC arm as a whole. The Company note that receipt of subsequent immunotherapy is not standard clinical practice in the UK, and this may also confound the results.
Table 2: Subsequent therapies received by patients in the nivolumab and Investigator’s Choice arms of the all-randomised and intended for docetaxel populations
<table>
<tr><th></th><th colspan="2">All-randomised</th><th colspan="2">Intended for docetaxel</th></tr>
<tr><th></th><th>Nivolumab</th><th>IC (N=121)</th><th>Nivolumab</th><th>Docetaxel</th></tr>
</table></td><td>Comment noted. The committee understood that a small number of people in the intention-to-treat arm switched to nivolumab in the extension phase of the trial. However, it noted the percentage of people who switched was low and therefore unlikely to have led to substantial bias Please see FAD sections 3.4 and 3.10.</td></tr>
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			[redacted]	
6.		Bristol Myers Squibb Pharmaceuticals Ltd	**Section 3.5 (page 9):** The Committee conclude that there is evidence of nivolumab's benefit for tumours with a PD-L1 score of 1% or higher, but at a lower PD-L1 score the benefit is not clear. In Section 3.24 (page 21) of the published guidance from the original appraisal, the Committee concluded that the cost-effectiveness results for the PD-L1 subgroups are not suitable for decision making, citing them to be "*subject to uncertainty because of the small patient numbers and because CheckMate-141 was not powered to show a difference between the PD-L1 subgroups*." Therefore, the Company are disappointed that the Committee have altered their conclusion on this topic, despite there being no change in the data available to inform it. Given this change in Committee conclusion, the Company would like to emphasise that CheckMate 141 was not powered to detect a difference between treatment arms in these subgroups, and that the patient numbers in these subgroups are small: [redacted] patients in the IC arm had confirmed PD-L1 <1%, of whom only [redacted] received docetaxel. As per the study protocol, these subgroups excluded patients in whom PD-L1 status could not be quantified; these patients represent 24% of the all-randomised population. Therefore, as well as the high degree of uncertainty introduced by small patient numbers in these groups, the exclusion of a substantial proportion of the study population from decision making could lead to patients within the NHS not having an effective treatment option available despite evidence in the all-randomised population indicating that they would benefit from nivolumab treatment. Furthermore, the use of these subgroups would provide insufficient evidence to address the decision problem of this appraisal as outlined in the final scope, which was to determine the clinical and cost-effectiveness of nivolumab within its anticipated marketing authorisation for treating recurrent or metastatic (R/M) squamous-cell carcinoma of the head and neck (SCCHN) after platinum-based therapy.[5] Furthermore, from the available data, the overlap between the 95% CI of HRs for nivolumab versus IC in the PD-L1 subgroups and the all-randomised population suggests that there is no statistically significant difference between the populations in terms of the treatment effect for OS (see Figure 4 in the original submission). Despite the 95% CIs overlapping 1 due to the small sample size, the point estimate of the HR indicates a treatment benefit with nivolumab versus IC (HR: 0.74) for the PD-L1 <1% subgroup. The Company welcome the Committee's acknowledgement of the feedback from the clinical expert that suggested PD-L1 score may not be a good predictor of treatment outcomes. As outlined in Comment 1, a significant unmet need irrespective of PD-L1 status remains in patients who would be eligible to receive nivolumab. Given the unmet need and the uncertainty associated with the results from the subgroup analyses based on PD-L1 expression, the all-	Comment noted. The committee concluded there is evidence that nivolumab is clinically beneficial for tumours with a PD-L1 score of 1% and above, but the benefit for those with a lower PD-L1 score is less certain. It acknowledged the uncertainty of the PD-L1 subgroup analysis, however considered analysis by PD-L1 subgroup were of interest and would be considered in its decision making. Please see FAD section 3.5 and 3.14.

[redacted]

	(N=240)		(N=[redacted])	(N=[redacted])
Cross-over to nivolumab, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any subsequent systemic therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Folic acid analogues	[redacted]	[redacted]	[redacted]	[redacted]
Other monoclonal antibodies [a]	[redacted]	[redacted]	[redacted]	[redacted]
Other immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy [b]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Taxanes	[redacted]	[redacted]	[redacted]	[redacted]

[a] Includes any monoclonal antibody except for nivolumab. [b] Includes both approved and experimental drugs.
Abbreviations: IC: Investigator's Choice.

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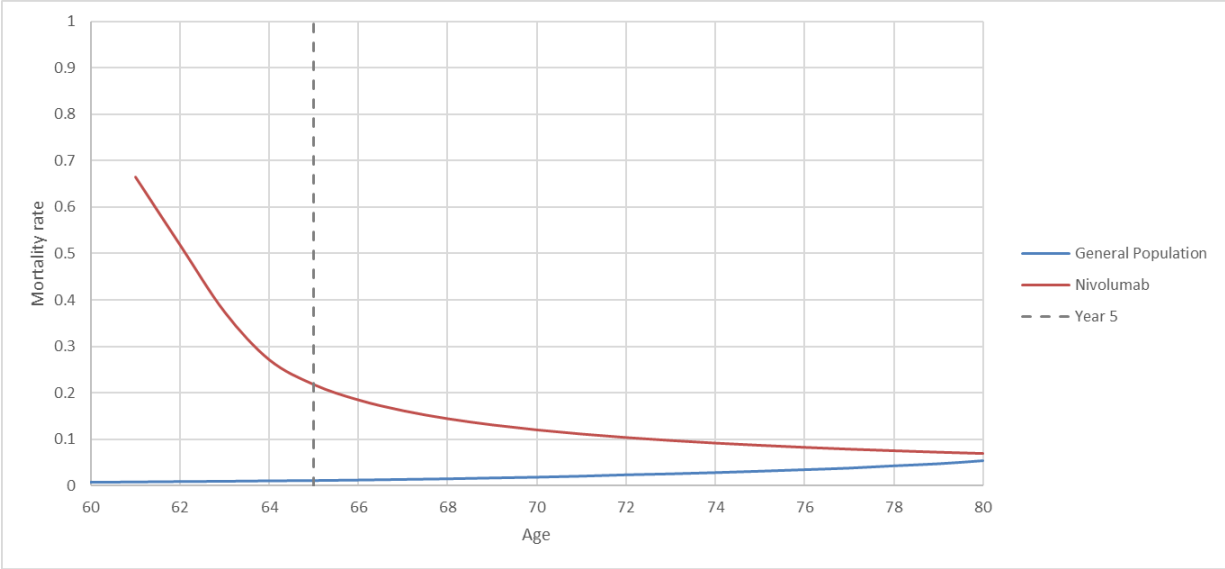
			randomised population should be considered as the patient population within the CDF review.	
7.		Bristol Myers Squibb Pharmaceuticals Ltd	**Section 3.7 (page 11):** The ACD states: "*the extrapolation of overall survival for the [intended for] docetaxel subgroup was uncertain because the assumptions had not been validated and reported with sufficient transparency*" and **Section 3.8 (page 11)** states: "*The most plausible extrapolation method for time to treatment discontinuation for the [intended for] docetaxel subgroup is unknown*". As outlined in Comment 2, the all-randomised population from the CheckMate 141 trial is the most appropriate data source for this appraisal, as it is adequately powered to detect differences between treatment arms and is most reflective of patients in this indication. However, for transparency, a detailed description of the survival analyses explored for the intended for docetaxel subgroup have been presented in **Error! Reference source not found.** of this response document. Cost-effectiveness results for a variety of plausible extrapolation methods for OS and time to treatment discontinuation (TTD) have been presented in **Error! Reference source not found.**, as requested by the Committee. **Section 3.15 (page 16)**: The ACD notes that *"the committee agreed that the PD-L1 subgroups are of interest within the docetaxel population."* As outlined in Comment 2, the all-randomised population from the CheckMate 141 trial is the most appropriate data source for this appraisal. Additionally, the Committee fail to acknowledge that robust subgroup analyses by PD-L1 expression status within the intended for docetaxel subgroup are not feasible, given the small patient numbers within these groups. As presented in the Company response to Technical Engagement, in the intended for docetaxel subgroup, [redacted] patients had PD-L1 <1% ([redacted] received nivolumab and [redacted] received docetaxel) and [redacted] had PD-L1 ≥1% ([redacted] received nivolumab and [redacted] received docetaxel). Given the high degree of uncertainty introduced by the extremely small numbers of patients in each treatment arm within these subgroups, as well as the risk of selection bias due to broken randomisation, cost effectiveness results suitable for decision-making cannot be generated from these data. In particular, the Company note that, as outlined in Comment 5, the Committee originally identified the small patient numbers and lack of suitable statistical powering in the PD-L1 subgroups to render cost-effectiveness analyses in these subgroups to be unsuitable for decision making. It follows that the analysis of subgroups within these subgroups would be subject to even more uncertainty and are thus similarly inappropriate for decision making.	Comment noted. The committee welcomed the analyses for overall survival and time to treatment discontinuation provided by the company. The FAD has been amended to reflect this - please see FAD section 3.7 and 3.8.
8.		Bristol Myers Squibb Pharmaceuticals Ltd	**Section 3.10 (page 13):** The ACD summarises the Committee's discussion surrounding the duration of treatment benefit of nivolumab. In **Section 3.15 (page 15–16)** the Committee conclude that their preferred approach to modelling includes an assumption of no treatment benefit for nivolumab 5 years after start of treatment and exclusion of a stopping rule. The Company are disappointed that important evidence was omitted from this discussion, which has led to a misunderstanding surrounding the treatment benefit of nivolumab when no stopping rule is applied. As per the Company response to Technical Engagement, inspection of the log cumulative hazards plot for OS (Figure 13 of the original Company submission) clearly shows that towards the end of the observed follow-up period for CheckMate 141 there was a difference between treatment arms in the change in hazards over time, with a reduction in the hazard over time in the nivolumab arm and a relatively constant hazard in the IC arm. It is therefore not appropriate to assume that the hazard in the nivolumab arm becomes equal to the IC arm (i.e. there is no treatment benefit for nivolumab in the long term). This is consistent with the TA490 Committee's preference for the use of piecewise models to extrapolate OS, which are recommended in NICE Technical Support Document (TSD) 14 for modelling datasets in which variable hazards are observed over time. Given the maturity of the data from the CheckMate 141 trial (minimum follow-up of 48.2 months), and the fact that piecewise models were used to extrapolate OS, applying an additional treatment waning assumption in scenarios where no stopping rule is employed is counterintuitive. Accordingly, on Section 3.9 (page 12) of the ACD, it is noted that *"a clinical expert explained that people who are*	Comment noted. The committee considered the revised 5-year stopping rule provided by the company. However, it felt a stopping rule in general was inappropriate and preferred analyses without a stopping rule. Please see FAD section 3.9. The committee also determined that

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
			alive 5 years after treatment started are considered 'cured' from the disease." Applying a treatment waning assumption from 5 years in the absence of a stopping rule is therefore not consistent with clinical reality, given patients alive at 5 years could be assumed to have a similar mortality risk to that of the general population. An updated plot of smoothed hazards over time (in months) is presented in Figure 3 (nivolumab and IC; all-randomised population), where a more appropriate scale has been applied. The plot shows a steeper reduction in hazards being observed in the IC arm compared to the nivolumab arm, and the curves have not yet converged. For the reasons outlined above, it is therefore not appropriate to apply a treatment waning assumption when no stopping rule is employed. **Figure 3: Smoothed hazards plot for nivolumab and IC overall survival (all-randomised population)**  **Abbreviations:** IC: investigator's choice.	continued treatment benefit up to 5 years is plausible. Please see FAD section 3.10.
9.		Bristol Myers Squibb Pharmaceuticals Ltd	**Section 3.10 (page 13):** The ACD notes that *"the committee considered that implementing a 2-year stopping rule for nivolumab could affect the relative treatment effect and cause the hazard rates to converge more quickly."* The Company would like to note that, as discussed further in Comment 7 and illustrated in Figure 3, convergence of the overall survival hazard rates for nivolumab IC has been misunderstood by the Committee. A difference between treatment arms in the change in hazards over time was observed towards the end of the follow-up period for CheckMate 141, indicating that hazard rates were not converging. As per the Company response to Technical Engagement, there is accumulating evidence to suggest that treatment	Comment noted. The committee considered there to be no clinical evidence that nivolumab can be curative. It also

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
			with PD-L1 inhibitors, including nivolumab, may facilitate longer term benefit even following treatment discontinuation. In the CheckMate 141 trial, [redacted] of the 13 patients in the nivolumab arm who were alive and in follow-up at the time of the latest data cut [redacted]. In addition, the Company note that implementation of a stopping rule is in line with the recommendation for pembrolizumab in the same indication (where a two year stopping rule was accepted as appropriate by the Committee) and with recommendations for nivolumab in other indications.[2, 6, 7] Given that clinical expert opinion suggests that patients who are in remission following treatment with nivolumab for five years may be considered functionally cured (ACD, Section 3.9), the Company present a revised base case in which a five-year stopping rule is implemented without a treatment waning assumption (full details of the revised base case are presented in **Error! Reference source not found.**). As discussed in Comment 7, applying a treatment waning assumption from 5 years in the absence of a stopping rule is not consistent with clinical reality, and is not supported by the data from the CheckMate 141 trial. Since patients in remission following treatment with nivolumab at the five year timepoints could be considered functionally cured, these arguments also apply when a 5 year stopping rule is implemented. As shown in Figure 4, in the revised Company base case the mortality rate associated with nivolumab is consistently higher than the mortality rate of the general population. As such, the survival for patients who are alive beyond the 5-year time point (and are considered functionally cured) may be underestimated in the base case, and thus the Company maintain that these base case assumptions are conservative. **Figure 4: Mortality rate for the general population and nivolumab treatment arm of the CheckMate 141 trial over the model horizon in the revised Company base case**  Full details of the revised Company base case are presented in **Error! Reference source not found.**. The cost-effectiveness results of the revised company base case including the 5-year stopping rule and no treatment waning are presented in Table 3, including scenario analyses with the PD-L1 subgroups and when no stopping rule	noted that there was no stopping rule included in CheckMate141 and therefore a stopping rule is not appropriate. Please see FAD sections 3.9 and 3.10.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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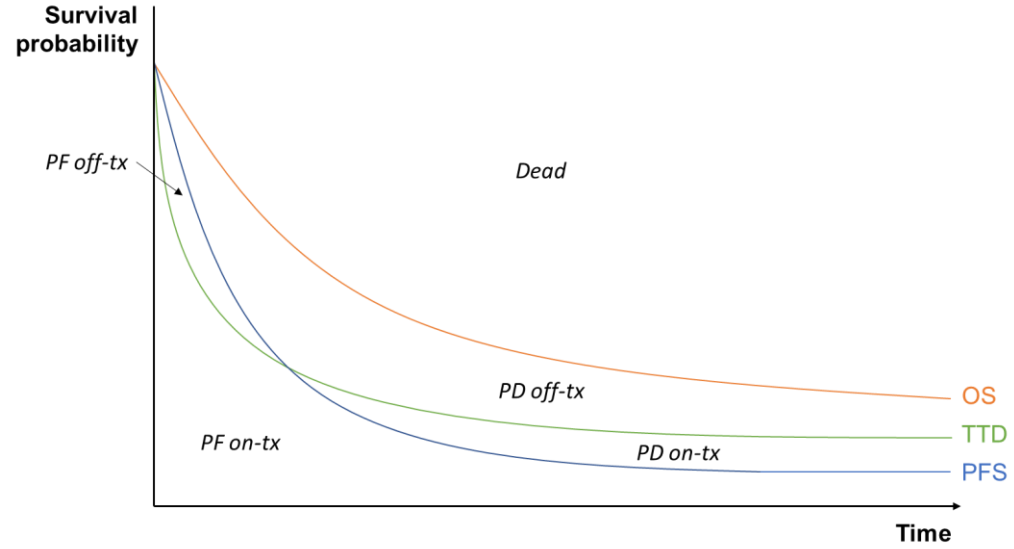
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>has been applied. Despite the fact that long-term survival for patients on nivolumab could be underestimated in the model, these results show that nivolumab is cost effective upon implementation of a five-year stopping rule, demonstrating it to be cost-effective use of NHS resources. Even when no stopping rule is applied, nivolumab remains cost-effective. For reference, the cost-effectiveness results for a variety of scenario combinations of stopping rules, treatment waning assumptions and utility assumptions in these populations are presented in Error! Reference source not found., the majority of which produce ICERs of less than £50,000/QALY.
Table 3: Cost-effectiveness results for the revised Company base case and one scenario combination of a treatment stopping rule and treatment waning assumption
<table>
<tr><th>Assumptions</th><th>ICER versus docetaxel (£/QALY)</th></tr>
<tr><td colspan="2">All-randomised population</td></tr>
<tr><td>5-year stopping rule, no treatment waning
(Revised Company base case)</td><td>43,207</td></tr>
<tr><td>No stopping rule, no treatment waning</td><td>48,442</td></tr>
<tr><td colspan="2">PD-L1 ≥1%</td></tr>
<tr><td>5-year stopping rule, no treatment waning</td><td>41,753</td></tr>
<tr><td>No stopping rule, no treatment waning</td><td>46,121</td></tr>
<tr><td colspan="2">PD-L1 <1%</td></tr>
<tr><td>5-year stopping rule, no treatment waning</td><td>48,576</td></tr>
<tr><td>No stopping rule, no treatment waning</td><td>48,576</td></tr>
</table>
Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9. Full details of the revised Company base case are presented in Error! Reference source not found..
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.</td><td></td></tr>
<tr><td>10.</td><td></td><td>Bristol Myers Squibb Pharmaceuticals Ltd</td><td>Section 3.11 (page 14): The ACD notes that “because no new evidence was presented on quality of life, the committee concluded that the most appropriate approach was to use both treatment-dependent and treatment-independent values in the base-case analysis.”
As discussed in response to ERG clarification question B7, no new analysis of utility data was conducted for the latest data cut of the Checkmate 141 trial, given that very few patients in either arm had remained in the trial and completed additional EQ-5D assessments. The Company acknowledge that uncertainty therefore remains in the most appropriate utility values for the model and that these values probably lie between the treatment-dependent and the treatment-independent estimates.
As described in the response to Technical Engagement, clinical expert feedback suggested that patients who remain on nivolumab for more than a few months and respond well to treatment are more likely to experience a utility benefit post-progression. The overall response rate (ORR) in CheckMate 141 was greater for nivolumab compared to IC (13.3% versus 5.8%), with a higher proportion of patients in the nivolumab arm achieving a best overall response of either a complete or partial response, as compared to the IC arm.[8] Nivolumab also offers a more durable response compared to IC, with responses maintained beyond 40 weeks for some patients in the nivolumab arm.[8] Therefore, whilst it is recognised that some patients receiving nivolumab may discontinue treatment or progress quickly (and therefore may be expected to have similar utility post-progression to patients who receive IC), the true utility values for the cohort as a whole may lie closer to treatment-dependent than to treatment-independent values.
In addition, the mixed model that included progression status and treatment arm (used to derive treatment-specific</td><td>Comment noted. The committee noted the updated utility estimate model provided by the company. Please see FAD section 3.11.</td></tr>
</table>

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

utility values) was associated with a better statistical fit than the model including progression status alone (treatment-independent utility values). The ERG highlighted in their comments on the Company Technical Engagement response that regression Model 1 and Model 2 (which include a covariate for being off treatment), are associated with even better statistical fit. This approach has previously been accepted by NICE in an oncology indication.[9] Model 2 was considered to lack face validity since it does not include a parameter for progression status.

A visual representation of the full model (Model 1), which includes progression status, treatment arm and treatment status, is presented in Figure 5. The derived utilities are presented in Table 4. Whilst this model still predicts a difference in utility between the "PD off-treatment" states for patients receiving nivolumab and IC, this difference is reduced compared to the model used to derive treatment-specific utility values. As such, the Company have updated their preferred base case to include utility values derived from the full model (Model 1), but for all scenarios presented in this response, results in which treatment-dependent and treatment-independent utility values are presented in **Error! Reference source not found.** for the Committee's consideration. Estimated utility decrements related to time before death have been excluded in line with the Committee's preferred assumptions.

Figure 5: Visual representation of the full utility model



Abbreviations: OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; TTD: time to treatment discontinuation; tx: treatment.

Table 4: Utility values derived from Model 1 (full model)

	Nivolumab		IC	
	On-treatment	Off-treatment	On-treatment	Off-treatment
PF	[redacted]	[redacted]	[redacted]	[redacted]

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>PD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: IC: investigator's choice; PD: progressed disease; PF: progression-free.
</td><td></td></tr>
<tr><td>11.</td><td></td><td>Bristol Myers Squibb Pharmaceuticals Ltd</td><td>
Section 3.13 (page 14): The ACD states that "based on the evidence provided, the committee concluded that it is uncertain whether nivolumab would extend life by more than 3 months compared with NHS standard care. Therefore, it is currently uncertain if nivolumab meets the end-of-life criteria when compared with docetaxel." Section 3.14 (page 15): The ACD further notes that "The model estimates for the mean overall-survival benefit are 12 months for the PD-L1 1% and above subgroup, and 6.3 months for the PD-L1 less than 1% subgroup. Because of the uncertainty in the clinical evidence for the PD-L1 less than 1% subgroup, the committee concluded that it is uncertain whether the life-extending criterion was met in that subgroup."
As discussed further in Comment 2, the Company consider the all-randomised population to be the most relevant for this appraisal. In this population, the data confirm that nivolumab meets the end of life criteria as compared with IC. This conclusion was not identified as an area of uncertainty in the original appraisal process (TA490) where it was accepted by the Committee, and remains valid in the revised Company base case (see Error! Reference source not found.) where the estimated survival benefit for nivolumab as compared with IC is 5.4 months.[4] Therefore, the Company are disappointed that the Committee have changed their conclusion despite no change in the source of data informing the end of life criteria decision.
A detailed description of the survival analyses explored for the intended for docetaxel subgroup has been provided in Error! Reference source not found. of this response document, which should resolve any uncertainty in the extrapolations of OS and TTD. The ACD reports that the mean OS benefit for nivolumab was estimated to be [redacted] months in the intended for docetaxel subgroup. It appears this result has been calculated based on the discounted life years gained (LYG); survival benefit should in fact be based on undiscounted LYG.
Mean survival for nivolumab and the comparator in the docetaxel and PD-L1 <1% subgroups using a range of extrapolation methods for OS are presented in Error! Reference source not found., alongside the estimated survival benefit for nivolumab. In both subgroups, nivolumab is associated with a survival benefit of considerably more than 3 months versus IC for all OS extrapolations explored. Whilst uncertainty remains in the underlying data for these subgroups given they are derived from small sample sizes, the durability in the survival benefit across a range of extrapolation methods confirm that nivolumab meets the end-of-life criteria within these subgroups.
Table 5: Estimated survival benefit for nivolumab for a variety of extrapolation methods
<table>
<tr><th rowspan="2">Extrapolation method for OS [a]</th><th colspan="2">Mean survival (months)</th><th rowspan="2">Survival benefit for nivolumab (months)</th></tr>
<tr><th>Nivolumab</th><th>IC/docetaxel</th></tr>
<tr><td>Intended for docetaxel subgroup</td><td></td><td></td><td></td></tr>
<tr><td>Piecewise lognormal 96-week cut-off</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Piecewise lognormal 48-week cut-off</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Fully parametric lognormal</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Fully parametric loglogistic</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>PD-L1 <1% subgroup</td><td></td><td></td><td></td></tr>
<tr><td>Piecewise lognormal 48-week cut-off</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Fully parametric lognormal</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Fully parametric loglogistic</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
[a] In the docetaxel subgroup, the exploratory extrapolation method for OS was applied to both the nivolumab and IC treatment arms. In the PD-L1 <1% subgroup, the exploratory extrapolation method for OS was applied to the nivolumab treatment arm only, given that [redacted]
</td><td>Comment noted. The Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. The Committee concluded that nivolumab fulfilled the end-of-life criteria. Please see FAD sections 3.12 and 3.13.</td></tr>
</table>

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
			[redacted]	
12.		Clinical expert	I am very disappointed in the decision to de-list Nivolumab for the treatment of patients with recurrent/metastatic head and neck cancer previously treated within 6 month with platinum base chemotherapy. Nivolumab is a significant improvement in our ability to treat these patients over the existing treatment options. It is a well-tolerated treatment that extends survival in a significant number of patients and is the first treatment that has shown a survival benefit for patients who have progressed after platinum containing therapy. I think the committee has failed to understand 2 important points that support the use of Nivolumab which I will discuss below.	Comment noted.
13.		Clinical expert	**The committee agreed that most people who will be eligible for immunotherapy in later lines of treatment will have a PD-L1 score of less than 1** In paragraph 3.2 of the consultation appraisal document it is discussed that Cetuximab therapy and Pembrolizumab therapy have changed the treatment paradigm. In particular it is asserted that because Pembrolizumab is used earlier in the treatment pathway it will lead to the use of Nivolumab mainly in patients who are PD-L1 <1% ("The committee agreed that most people who will be eligible for immunotherapy in later lines of treatment will have a PD-L1 score of less than 1"). This is factually incorrect. In my practice (one of the largest, if not the largest, in the UK) 40% of patients are eligible for Nivolumab when they have relapsed within 6 months of chemo-radiotherapy with platinum. These patients are not exclusively PD-L1 <1%, in fact we know that the large majority of them are PD-L1 >1%. It is therefore incorrect to say that Nivolumab would be reserved largely for the treatment of PD-L1 <1% patients. Nivolumab would be used for patients with all levels of PD-L1, but the great majority of them would be >1%.	Comment noted. The committee concluded there is evidence that nivolumab is clinically beneficial for tumours with a PD-L1 score of 1% and above, but the benefit for those with a lower PD-L1 score is less certain. It acknowledged the uncertainty of the PD-L1 subgroup analysis, however considered analysis by PD-L1 subgroup were of interest and would be considered in its decision making. Please see FAD section 3.5 and 3.14.
14.		Clinical expert	**The comparison with the docetaxel subgroup from CheckMate 141 is most relevant to UK clinical practice.** The comparison with Docetaxel is discussed in paragraphs 3.3 and 3.4, where it is stated that "the clinical benefit of Nivolumab compared to Docetaxel alone is not clear". I believe that the committee is mistaken in trying to compare Nivolumab with the Docetaxel subgroup. Docetaxel is an intensive regime with significant toxicity. In the real world outside the trial setting, very few patients with recurrent/metastatic head and neck cancer are able to tolerate treatment with Docetaxel. Prior to Nivolumab my centre would treat <5 patients per year with Docetaxel. Patients who were treated would rarely receive beyond 3 cycles because of the significant haematological toxicity associated with	Comment noted. The committee concluded that the most appropriate data source for this review is the intention-to-treat

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
			the drug. Patients over the age of 70 were especially likely to experience toxicity, limiting its use to younger patients. In comparison we treat 30+ new patents with Nivolumab which is significantly better tolerated. Especially by patients in the over 70 age group. Patients have to be ECOG PS 0-1 to receive Nivolumab and it is noted that there was no significant difference between PS scores in the 3 different IC treatment groups. However while ECOG PS is very useful in many respects it can hide significant differences in ability to tolerate treatment. Not all PS 1 patients are the same (For example PS hides the effect of age eg. a PS 1 80yr old will not tolerate Docetaxel while a PS 1 60yr old might). Unfortunately it is well recognised that clinical trials are not representative of patients in the real world. What is especially impressive however is how well the results of treating patients with Nivolumab do translate to the clinic. Both the CDF follow up data and my own audit show that the results in the real world match those of CheckMate 141. In reality, the real world comparator is best supportive care, but in the absence of this in a clinical trial the ITT group should be used rather than the Docetaxel subgroup.	population, but the docetaxel subgroup analysis should also be considered. The FAD has been amended to reflect this - please see FAD section 3.3.
15.		Head And Neck Cancer UK (HANCUK)	Insofar as the comments from HANCUK and the oral evidence presented at Committee are concerned, the report presents a fair and balanced summary.	Comment noted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nivolumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

Has all of the relevant evidence been taken into account?
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Are the recommendations sound and a suitable basis for guidance to the NHS?
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: December 2020

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
At that meeting, the committee will also consider comments made by people who are not consultees.
After considering these comments, the committee will prepare the final appraisal document.

- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using nivolumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 28 January 2021

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 Nivolumab is not recommended, within its marketing authorisation, for treating recurrent or metastatic squamous cell carcinoma of the head and neck in adults whose disease has progressed during or after platinum-based chemotherapy.

1.2 This recommendation is not intended to affect treatment with nivolumab that was started in the NHS before this guidance was published. People having treatment outside of this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for nivolumab for treating recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy (NICE technology appraisal guidance 490). If nivolumab is not recommended for routine commissioning in this indication when final guidance is published, it will no longer be available in the Cancer Drugs Fund for people to start treatment, but people already taking it will be able to continue.

The new evidence includes data from clinical trials and from patients having treatment in the NHS, while this treatment was available in the Cancer Drugs Fund in England. It shows that people who have nivolumab are likely to live up to 9 months longer than those who have docetaxel, methotrexate or cetuximab. But it is unclear whether nivolumab extends life for longer than 3 months in people who are fit enough to be offered docetaxel or for people with tumours with a low PD-L1 score. These groups of people are most likely to be offered nivolumab in the NHS. So it is unclear whether nivolumab meets NICE's criteria to be considered a life-extending treatment.

The cost-effectiveness estimates are highly uncertain. But they are likely to be at the higher end of what NICE considers an acceptable use of NHS resources, and could exceed the maximum. So nivolumab is not recommended.

2 Information about nivolumab

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol-Myers Squibb) as monotherapy is indicated for 'the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price is £439 per 40-mg vial, £1,097 per 100-mg vial and £2,633 per 240-mg vial (excluding VAT; British national formulary [BNF] online accessed November 2020 and company submission). The company has a commercial arrangement. This makes nivolumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Bristol-Myers Squibb, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

This guidance review looks at data collected in the Cancer Drugs Fund to address uncertainties identified during the original appraisal. Further information about the

original appraisal is in the committee papers. As a condition of the Cancer Drugs Fund funding and the managed access arrangement, the company was required to collect updated efficacy data from the CheckMate 141 study. Data were also collected using the Systemic Anti-Cancer Therapy (SACT) dataset.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, page 8), and took these into account in its decision making. The committee discussed the following issues, which were outstanding after the technical engagement stage:

- the generalisability of the trial population to NHS clinical practice
- the choice of parametric models to predict overall survival
- the choice of parametric models to predict time to treatment discontinuation
- the 2-year stopping rule and the continued duration of treatment benefit if nivolumab were to be stopped at 2 years
- the choice of utility values
- the cost effectiveness in the PD-L1 subgroups.

The condition and clinical management

Squamous cell carcinoma of the head and neck is a debilitating condition with an unmet need for effective treatment options

3.1 Recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) that has progressed during or after platinum-based chemotherapy has a poor prognosis. The patient experts described SCCHN as a debilitating condition with multiple distressing symptoms such as disfigurement, a dry and sore mouth, weight loss and decreased appetite. They explained that the disease affects all aspects of life including mental wellbeing, social functioning, mobility and work. The clinical expert explained that people have limited treatment options and their disease is generally considered incurable at this stage. Existing treatments are taxane-based chemotherapies such as docetaxel or paclitaxel, which can cause significant adverse reactions. The patient

expert stated that the outlook is poor for patients with recurrent or metastatic SCCHN that has relapsed on or after platinum-based chemotherapy. The committee noted that improved quality of life both during and after treatment is most important to this patient group, as is extending life. The committee concluded that there is an unmet need for effective treatment options for people with recurrent or metastatic SCCHN that has progressed on or after platinum-based chemotherapy.

Docetaxel is the most appropriate comparator for people fit enough to have it

3.2 The committee noted that the treatment pathway for recurrent or metastatic SCCHN had changed since the publication of the original appraisal of nivolumab. This is because cetuximab combination therapy and pembrolizumab monotherapy have been recommended for treating recurrent or metastatic SCCHN (see NICE's technology appraisal guidance on cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck and pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma). The committee noted that both these treatments are used earlier in the treatment pathway than nivolumab. It also noted that there are potential implications for using nivolumab to treat SCCHN that has progressed within 6 months of platinum-based chemotherapy. Pembrolizumab is recommended for untreated metastatic or unresectable recurrent SCCHN in adults whose tumours express PD-L1 with a combined positive score of 1 or more. But in NHS clinical practice, people would only have immunotherapy once during the treatment pathway. Therefore, the committee agreed that most people who will be eligible for immunotherapy in later lines of treatment will have tumours that have a PD-L1 score of less than 1. At the time of the original appraisal of nivolumab, treatment options in clinical practice in England included taxane-based chemotherapies (such as docetaxel and paclitaxel) or methotrexate. In the original appraisal, the clinical experts agreed that although there was no

evidence of difference in efficacy between docetaxel and paclitaxel, docetaxel would be the standard single-agent chemotherapy used for recurrent or metastatic SCCHN that progressed during or after platinum-based therapy in the NHS (most often prescribed as a 3-weekly treatment regimen), and that the use of paclitaxel in clinical practice is limited. They also stated that methotrexate is normally only offered to people with a poor performance status who are not fit enough to have a taxane, or as subsequent therapy for people who have had a single-agent taxane. The committee concluded in the original appraisal that docetaxel would be the most appropriate comparator for people fit enough to have it. For this guidance review, the committee concluded that docetaxel was still the most appropriate comparator for its decision making.

Clinical effectiveness

The docetaxel subgroup from CheckMate 141 is most relevant to UK clinical practice

3.3 The clinical-effectiveness evidence for nivolumab came from 1 study (CheckMate 141) that compared nivolumab with the investigator's choice of therapy. Patients randomised to the investigator-choice arm had 1 of 3 possible weekly therapies (docetaxel [47% of patients], methotrexate [41%] and cetuximab [12%]). In the original appraisal, the committee concluded that excluding paclitaxel from the trial and including cetuximab, a drug not used in clinical practice at that time and therefore not included in the NICE scope, introduced uncertainty about the relevance of CheckMate 141 to UK clinical practice. The committee also concluded, based on the testimony of the clinical experts, that it was valid to assume that docetaxel and paclitaxel were equivalent. But it was not persuaded by the company's assumption that docetaxel is equivalent to methotrexate. For this guidance review, the clinical expert acknowledged that the trial took place in several countries where standard care differs from NHS clinical practice. He suggested that the investigator-choice arm of the trial was an appropriate comparison even though cetuximab is not standard

care in NHS clinical practice and methotrexate is only offered to people with poor performance status and may be less effective. The Cancer Drugs Fund Clinical Lead stated that people in the trial (who had an Eastern Cooperative Oncology Group performance status of 0 or 1) would have been fit enough to get docetaxel in NHS clinical practice, and therefore the investigator-choice arm would not be a relevant comparator. The committee noted that the company had presented results for an analysis comparing nivolumab and docetaxel in patients who would have docetaxel (referred to as the 'docetaxel subgroup') in CheckMate 141. The company highlighted that the trial was not powered to detect differences between nivolumab and docetaxel alone and therefore any results had to be treated with caution. The committee acknowledged that this was not a prespecified subgroup analysis and such a comparison was less robust than using the intention-to-treat population, because of the smaller sample size. The committee agreed that there was uncertainty about the relevance of the comparator arm of CheckMate 141 to UK clinical practice. It concluded that the docetaxel subgroup was the most appropriate data source for this guidance review because it was most relevant to NHS clinical practice.

The clinical benefit of nivolumab compared with docetaxel alone is not clear

3.4 For this guidance review, the company provided an additional 37 months of data (up to October 2019) from Checkmate 141. The results for the intention-to-treat population showed that people who had nivolumab lived longer than people who had the investigator-choice treatment (median overall survival for nivolumab was 7.7 months, 95% confidence interval 5.7 to 8.7 months; investigator choice was 5.1 months, 95% confidence interval 4.0 to 6.2 months; hazard ratio 0.69, 95% confidence interval 0.55 to 0.86). The Cancer Drugs Fund Clinical Lead referred to an amendment update of the clinical protocol for CheckMate 141, which meant that people in the investigator-choice arm could have had nivolumab in the extension phase of the trial. The company did not provide data on how

many people switched from investigator choice to nivolumab. It is therefore unclear how a treatment switch would have affected overall survival, which could potentially bias the results against nivolumab. The company provided results for the docetaxel subgroup that showed a numerical survival benefit for nivolumab compared with docetaxel, but this was not statistically significant (the exact data are confidential and cannot be reported here). The committee acknowledged that there was uncertainty associated with the results from the docetaxel subgroup because of the small number of people in the subgroup analysis, and because the effect of treatment switching was unknown. However, it agreed that the subgroup analysis was relevant for its decision making (see section 3.4). It concluded, based on the evidence that had been presented to date, that it was uncertain whether nivolumab was clinically effective compared with docetaxel alone.

There is evidence of nivolumab's benefit for tumours with a PD-L1 score of 1% or higher, but at a lower PD-L1 score the benefit is not clear

3.5 In the original appraisal, the committee concluded that there was evidence of nivolumab's benefit for tumours expressing 1% or more PD-L1 protein, but at lower expression levels the benefit was not clear. For this guidance review, the company provided subgroup analyses based on the latest available data (up to 15th October 2019) for PD-L1 of 1% and above and PD-L1 of less than 1% subgroups in the intention-to-treat population of CheckMate 141. For the subgroup with a PD-L1 score of 1% and above, the median overall-survival gain was 3.6 months with nivolumab compared with investigator choice (hazard ratio of 0.54, 95% confidence interval 0.39 to 0.76). For the less than 1% PD-L1 group, the median overall-survival gain was 1 month (hazard ratio 0.74, 95% confidence interval 0.50 to 1.10). The clinical expert explained that in clinical practice the availability of PD-L1 testing varies across the NHS in England, and that PD-L1 scores might not be available for all people at the time when treatment is started. The clinical expert also suggested that the PD-L1 score may not be as good a predictor of treatment outcome as previously

thought. The committee noted that PD-L1 testing in SCCHN would become routine in the NHS now that pembrolizumab is recommended for treating PD-L1 in adults whose tumours express 1% or more PD-L1. It acknowledged that there was uncertainty associated with the results from the subgroup analyses based on PD-L1 expression because of the small number of people in the subgroup analysis. However, it considered it was important to explore them because of NICE's recent recommendation for using pembrolizumab earlier in the treatment pathway, which means that nivolumab is likely to be used to treat SCCHN with a low PD-L1 score (see section 3.2). It concluded that there was evidence that nivolumab is clinically beneficial for tumours with a PD-L1 score of 1% and above but the benefit for those with a low PD-L1 score was less certain.

Clinical experience with nivolumab in the Cancer Drugs Fund reflects the trial results

3.6 As well as new data from the CheckMate 141 study, there were Systemic Anti-Cancer Therapy (SACT) data available for this review. These were collected from 506 people who had nivolumab through the Cancer Drugs Fund between October 2017 and October 2019. The clinical expert explained that the clinical experience with nivolumab is positive and that outcomes are reflective of what was seen in the clinical trials. The 1-year overall survival was similar between the nivolumab arm of the intention-to-treat population in the trial and the SACT data (trial 33.4%, 95% confidence interval 27.5 to 39.5; SACT data 34%, 95% confidence interval 29% to 38%). The median overall survival in the trial was longer (7.7 months, 95% confidence interval 5.7 to 8.7 months) than in the SACT data (6.5 months, 95% confidence interval 5.6 to 7.6 months). However, the 95% confidence intervals overlapped. The time to treatment discontinuation in the SACT data was 3.0 months (95% confidence interval 2.7 to 3.3 months), which is longer than in the trial (results are confidential and cannot be reported). The committee noted that the SACT data had a median follow-up of 6.2 months compared with a minimum follow up of 48.2 months in the trial.

Modelling overall survival and time to treatment discontinuation

The most plausible extrapolation method for overall survival for the docetaxel subgroup is unknown

3.7 In the original appraisal, the committee accepted that a piecewise model was appropriate for estimating overall survival in the intention-to-treat population. The model used Kaplan–Meier data followed by a log-normal distribution, but the time point from which to extrapolate was uncertain. For this guidance review, the company used data from the intention-to-treat population of the trial. It extrapolated from 96 weeks in line with the median follow up of the trial. This resulted in a 5-year survival of 5.7% and a 10-year survival of 2.6%. The clinical expert estimated that it was plausible that between 1% and 5% of people having nivolumab will be alive at 5 years, and that few people survive up to 10 years. In its response to technical engagement, the company used the same extrapolation method for the docetaxel subgroup. It did not present evidence of the goodness of fit for this method to the subgroup data, and it did not explore alternative methods. The committee considered the docetaxel subgroup to be the most appropriate data source for this guidance review because it was the most relevant population to NHS clinical practice. But it agreed that the extrapolation of overall survival for the docetaxel subgroup was uncertain because the assumptions had not been validated and reported with sufficient transparency.

The most plausible extrapolation method for time to treatment discontinuation for the docetaxel subgroup is unknown

3.8 In the original appraisal, using the intention-to-treat population, the committee concluded that none of the parametric distributions fitted the time to treatment-discontinuation data well. It preferred the generalised gamma distribution for both arms in the model for this population. In this guidance review, the company presented an alternative approach using different distributions for the 2 treatment arms. It used the 2-spline normal

distribution for the nivolumab arm, because it had a better statistical and visual fit to the data than the generalised gamma distribution. The method used for the investigator-choice arm is confidential and cannot be reported here. The ERG preferred to use the generalised gamma distribution for both arms as in the original appraisal and in line with the NICE Decision Support Unit's technical support document 14. In its response to technical engagement, the company used the same extrapolation method for the docetaxel subgroup. It did not present evidence of the goodness of fit for this method to the subgroup data and it did not explore alternative methods. The committee considered the docetaxel subgroup to be the most appropriate data source for this review because it was the most relevant population to NHS clinical practice. But it agreed that the time to treatment discontinuation for the docetaxel subgroup was uncertain.

Stopping rule and continued treatment effect

Analyses without a stopping rule are more appropriate for decision making

3.9 In the original appraisal, the committee concluded that analyses without a nivolumab stopping rule are more appropriate for decision-making than analyses that included a stopping rule. The 2-year stopping rule was only accepted in the context of the Cancer Drugs Fund. In this guidance review, the patient experts and the clinical expert agreed that people might be disappointed if treatment was beneficial but was stopped at 2 years. The clinical expert confirmed that people who tolerate and benefit from treatment should be able to have it until their disease progresses, or they have intolerable side effects or choose to stop. People who stopped nivolumab after 2 years but whose disease has not progressed would be offered platinum-based chemotherapy. The clinical expert explained that people who are alive 5 years after treatment started are considered 'cured' from the disease. The committee noted that there was no stopping rule included in the trial, and that some people were still taking nivolumab after 2 years. It noted that a stopping rule had been accepted in previous

appraisals for nivolumab and other similar drugs, whether or not it was included in the trial. However, in this instance, the committee concluded that a 2-year stopping rule was not appropriate.

Continued treatment benefit up to 5 years is plausible

3.10 In the original appraisal, the committee concluded that it was plausible that the treatment benefit of nivolumab continued for 5 years after treatment started. For this guidance review, the company provided a smoothed hazard-rates plot for overall survival for the intention-to-treat population for nivolumab and investigator choice. The plot suggested that the hazard rates seemed to meet at around 5 years. This indicates that there was no difference in the treatment effect of the 2 arms at 5 years. Therefore, the ERG included treatment waning at 5 years after the start of treatment in its base-case analysis. In the trial, people in the investigator-choice arm could have had nivolumab during the extension phase of the trial (see section 3.4). The committee acknowledged that this crossover could decrease the apparent relative effectiveness of nivolumab compared with investigator choice, but it had not been presented with evidence that it could consider as part of its decision making. Conversely, the committee considered that implementing a 2-year stopping rule for nivolumab could affect the relative treatment effect and cause the hazard rates to converge more quickly. It concluded that it was plausible that nivolumab's treatment effect matches that of standard care at 5 years after treatment started.

Utility values in the economic model

The most appropriate utility values lie between the treatment-dependent and the treatment-independent estimates

3.11 In the original appraisal, the committee agreed that the most appropriate utility estimates would lie between the treatment-dependent utilities and the treatment-independent utilities. The clinical expert explained that the effect on quality of life was similar for the different treatment options

available for recurrent and metastatic SCCHN. The patient experts and the clinical expert confirmed that people's quality of life diminishes during the last months of life. Because no new evidence was presented on quality of life, the committee concluded that the most appropriate approach was to use both treatment-dependent and treatment-independent values in the base-case analysis.

End of life

Life expectancy for people with recurrent or metastatic SCCHN is less than 24 months

3.12 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. In the original appraisal, the data showed that life expectancy for people with SCCHN that has progressed within 6 months of platinum-based chemotherapy was less than 24 months. The committee did not hear any evidence to change this conclusion. Therefore, it concluded that nivolumab met the short life-expectancy criterion.

It is unclear whether nivolumab meets the end-of-life criteria when compared with docetaxel

3.13 In the latest data available for CheckMate 141, the median overall survival for the intention-to-treat population for nivolumab was 7.7 months (95% confidence interval 5.7 to 8.7 months) compared with 5.1 months (95% confidence interval 4.0 to 6.2 months) for investigator choice. The model predicted a mean survival benefit for nivolumab of between 6.8 and 9.2 months in this population. The median overall-survival results for the docetaxel subgroup are confidential and cannot be reported here. When the docetaxel subgroup data were used in the company's base-case model, the mean overall-survival benefit for nivolumab was estimated to be 6.7 months. The committee noted that the clinical effectiveness of nivolumab was uncertain in this population (see section 3.4). Also, the

extrapolation methods used for overall survival and time to treatment discontinuation were uncertain (see section 3.7 and section 3.8). Based on the evidence provided, the committee concluded that it is uncertain whether nivolumab would extend life by more than 3 months compared with NHS standard care. Therefore, it is currently uncertain if nivolumab meets the end-of-life criteria when compared with docetaxel.

Nivolumab's life-extending benefit for tumours with a low PD-L1 score is unclear

3.14 In the latest data available for CheckMate 141, nivolumab increased median overall survival by more than 3 months compared with investigator choice in people whose tumours had a PD-L1 score of 1% and above (see section 3.5). In people whose tumours had a PD-L1 score of less than 1% the increase in median survival was only 1 month, and this was not statistically significant (see section 3.5). The model estimates for the mean overall-survival benefit are 12 months for the PD-L1 1% and above subgroup, and 6.3 months for the PD-L1 less than 1% subgroup. Because of the uncertainty in the clinical evidence for the PD-L1 less than 1% subgroup, the committee concluded that it is uncertain whether the life-extending criterion was met in that subgroup.

Cost effectiveness

The company's base case does not reflect the committee's preferred assumptions

3.15 The committee agreed that its preferred approach to modelling would:

- include data from the docetaxel subgroup only
- include treatment-dependent and treatment-independent utility values
- assume no treatment benefit for nivolumab 5 years after start of treatment
- exclude the estimated utility decrements related to time before death

- exclude the stopping rule.

The company did not do exploratory analyses for the docetaxel subgroup data. And its extrapolation methods for overall survival, progression-free survival and time on treatment for this subgroup are unclear. So the ERG was unable to do exploratory analyses for the docetaxel subgroup. The committee would like to see scenarios in which the effect of different extrapolation methods are explored. Also, the committee agreed that the PD-L1 subgroups are of interest within the docetaxel population.

Because of the uncertainty an acceptable ICER is toward the lower end of the range normally considered a cost-effective use of NHS resources

3.16 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER and whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high level of uncertainty for the docetaxel subgroup specifically regarding the clinical effectiveness (see section 3.4), appropriate extrapolation methods (see section 3.6 and section 3.7) and the end-of-life criteria (see section 3.12).

It is unclear whether nivolumab would be a cost-effective use of NHS resources

3.17 The company's base-case assumptions differed from the committee's preferred assumptions. The company's base case included a lifetime treatment benefit of nivolumab, treatment-dependent utilities and a 2-year stopping rule. Also, the time to treatment discontinuation was extrapolated using different distributions in the 2 arms. The company's base-case ICER

was £37,257 per QALY gained in the intention-to-treat population. The ICER increased by £9,304 per QALY gained, to £46,540 per QALY gained, when both the stopping rule and the time-to-death disutility decrements were removed. It increased by £17,464 per QALY gained, to £54,700 per QALY gained, when the treatment-independent utility values were also applied. The ICER was £41,888 per QALY gained when the stopping rule and the time-to-death disutility decrements were removed, and the time to treatment discontinuation was extrapolated with the same distribution in the 2 arms. When the treatment-independent utility values were also applied, the ICER was £49,233 per QALY gained. The committee noted that the deterministic and probabilistic ICERs were similar. It also noted that the ICER in the docetaxel subgroup, which used the company's base-case assumptions, was £41,695 per QALY gained. This was £4,442 per QALY gained higher than in the intention-to-treat population. The committee agreed that it was unclear how the adjusted extrapolation methods for overall survival, progression-free survival and time to treatment discontinuation would affect the cost-effectiveness estimates in the docetaxel subgroup, and what the ICER would be for this subgroup if all of its preferred assumptions were included in the model. It also agreed that the most likely ICER could be £50,000 per QALY gained or higher, and that there was high uncertainty around this ICER. It concluded that it could not recommend nivolumab for routine use in the NHS because it was not presented with all the relevant evidence to conclude that nivolumab was a cost-effective use of NHS resources.

Cancer Drugs Fund

Nivolumab cannot be recommended in the Cancer Drugs Fund

3.18 The aim of a Cancer Drugs Fund guidance review is to decide whether or not the drug can be recommended for routine use. Nivolumab for SCCHN after platinum-based chemotherapy may not remain in the Cancer Drugs Fund once the guidance review has been completed (see section 6.19 of the guide to the processes of technology appraisal).

Equality issues

The recommendations apply equally to all people with SCCHN

3.19 A patient expert questioned whether there is an equality issue regarding age. The clinical expert confirmed that there is no age limit for treatment with nivolumab. The committee heard from the Cancer Drugs Fund clinical lead that data collected by Public Health England from NHS patients in England showed that many older patients had taken nivolumab while it was available in the Cancer Drugs Fund. The committee concluded that there was no relevant equalities issue.

Other factors

3.20 The company did not highlight any additional benefits that had not been captured in the QALY calculations.

Conclusion

Nivolumab is not recommended for routine commissioning

3.21 The committee could not recommend nivolumab, within its marketing authorisation, for recurrent or metastatic SCCHN after platinum-based chemotherapy in adults. In the original appraisal, the committee concluded that docetaxel was the most relevant comparator, and that assuming clinical equivalence between some of the comparators was uncertain. This meant that using investigator-choice data to model all comparators would be likely to underestimate the effectiveness of docetaxel. In this guidance review, the company did not present a comprehensive analysis for the docetaxel subgroup. Therefore, the committee was unable to determine the most plausible ICER for this population. Based on the ICERs for the intention-to-treat population, the committee agreed that the ICERs for the docetaxel subgroup are likely to be £50,000 per QALY gained or higher. Given the uncertainty about the clinical effectiveness and life-extending benefit of nivolumab compared

with docetaxel, this ICER is above what NICE considers an acceptable use of NHS resource.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Lindsay Smith
Chair, appraisal committee
December 2020

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Verena Wolfram
Technical lead

Nicola Hay
Technical adviser

Kate Moore
Project manager

ISBN: [to be added at publication]

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 28 January 2021 via NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bristol Myers Squibb Pharmaceuticals Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 28 January 2021 via NICE DOCS

	Bristol-Myers Squibb (BMS) Pharmaceuticals Limited would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for nivolumab for treating recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) after platinum-based chemotherapy [ID1585] (CDF Review of TA490). We are highly disappointed that the Appraisal Committee has ignored the clinical expert feedback 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. The unmet need in these patients has been heightened during the ongoing COVID-19 pandemic: in the UK between March and May 2020, urgent referrals for people with a suspicion of head and neck cancer dropped by 59%, which is projected to significantly impact 5-year survival time in these patients.[1] We believe that the basis for this preliminary decision relies on the Committee reaching several conclusions directly in contradiction to those reached in the original appraisal (TA490) despite the data informing these issues remaining unchanged. In response to the ACD, BMS have presented a revised economic base case to address the Committee's concerns regarding the suitability of implementing a 2-year stopping rule for nivolumab treatment. This revised base case is associated with an incremental cost-effectiveness ratio (ICER) below the willingness-to-pay threshold of £50,000 for medicines which reach the end-of-life criteria and thus demonstrates nivolumab to be a cost-effective use of NHS resources. 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 R/M SCCHN after platinum-based chemotherapy in UK clinical practice.
1	**Section 3.2 (page 6):** The Committee note that "*both [cetuximab combination therapy and pembrolizumab monotherapy] are used earlier in the treatment pathway than nivolumab*" and that *"pembrolizumab is recommended for untreated metastatic or unresectable recurrent SCCHN in adults whose tumours express PD-L1 with a combined positive score of 1 or more. But in NHS clinical practice, people would only have immunotherapy once during the treatment pathway. Therefore, the committee agreed that most people who will be eligible for immunotherapy in later lines of treatment will have tumours that have a PD-L1 score of less than 1."* Similar arguments are reported in Section 3.5 (page 9). The Committee have mis-represented the target population for this submission in the ACD. The Company maintain that there remains an unmet need in the indication of relevance for this submission for patients irrespective of programmed death ligand 1 (PD-L1) status. The indication of relevance for this submission is: "*nivolumab monotherapy for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) in adults progressing on or after platinum-based therapy*". As shown in Figure 1, this population includes patients who progress following platinum-based therapy in the recurrent or metastatic (R/M) setting and patients who progress following platinum-based therapy as part of an earlier-stage intervention for the treatment of locally advanced disease. Cetuximab in combination with platinum-based chemotherapy is recommended for treating recurrent or metastatic squamous cell cancer of the head and neck in cancers that started in the oral cavity, and pembrolizumab is recommended for untreated metastatic or unresectable recurrent SCCHN for patients whose tumours express PD-L1 with a combined positive score (CPS) of 1 or more (as

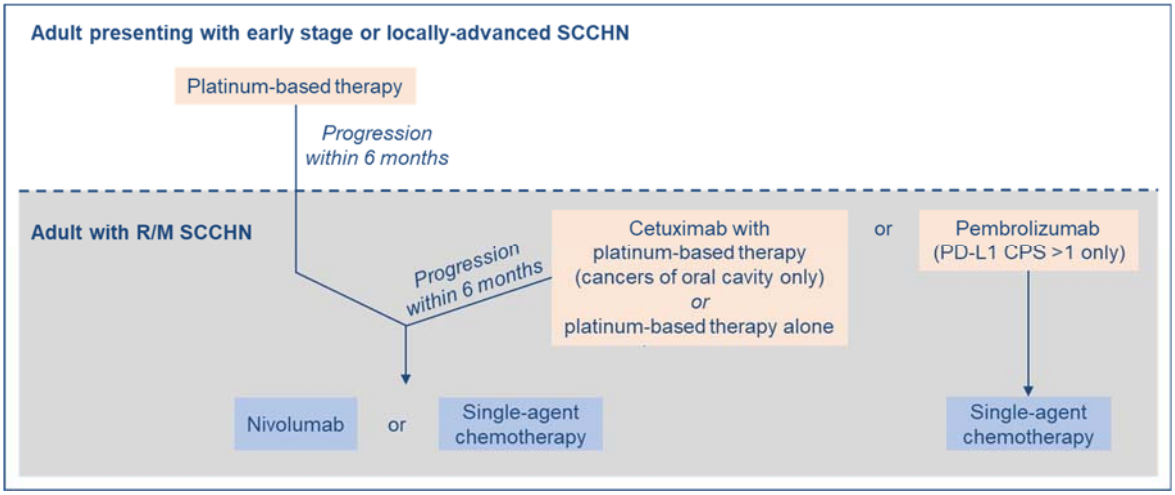
shown in Figure 1).[2, 3] As patients who have progressed following platinum-based therapy in the locally-advanced setting would be eligible for nivolumab first line in the R/M setting, the conclusion of the Committee that cetuximab and pembrolizumab are used earlier in the treatment pathway than nivolumab is incorrect, with all three eligible for first-line use in the R/M setting for some patients.

The Company agree that patients who receive pembrolizumab in the R/M setting would not receive nivolumab in a later line of treatment. However, nivolumab is available to patients who have progressed within 6 months of receiving platinum-based therapy in the locally advanced disease setting. For these patients, there may be a choice between receiving pembrolizumab in those who have PD-L1 >1%, cetuximab in those whose disease began in the oral cavity, or nivolumab in patients regardless of their PD-L1 status or disease origin location. Patients that progressed within 6 months of receiving platinum-based therapy in the locally advanced disease setting constitute a considerable proportion of patients eligible for nivolumab in clinical practice, with a clinical expert consulted as part of this response estimating this proportion to be 40% of patients.

Nivolumab would also remain the only immunotherapy option for patients who are PD-L1 <1%, or whose PD-L1 status cannot be determined. This includes patients for whom immediate treatment initiation is clinically necessary and thus PD-L1 status would not be ascertained prior to treatment commencement. In addition to the acknowledgement by the clinical expert in the ACD that the availability of PD-L1 testing varies across the NHS in England (Section 3.5, page 9), a clinical expert consulted as part of this response highlighted that obtaining the results of a PD-L1 test is highly variable between multidisciplinary teams and may take several weeks in UK clinical practice.

Therefore, the Company consider nivolumab would address a significant area of unmet need in UK clinical practice despite the introduction of cetuximab and pembrolizumab and regardless of PD-L1 status.

Figure 1: Clinical care pathway for adults with R/M SCCHN who have progressed after platinum-based therapy



Patients with SCCHN may receive platinum-based therapy first-line in the R/M setting or as part of an earlier-stage intervention for the treatment of locally advanced disease. In the R/M setting, patients with a combined positive score of 1 or more may receive pembrolizumab first-line and patients with cancer of the oral cavity may receive cetuximab.
Patients who may be considered eligible for treatment with nivolumab under the anticipated indication for SCCHN are expected to have progressed within 6 months of having received platinum-based therapy, but may have received this therapy in either setting.
Abbreviations: CPS: combined positive score; R/M: recurrent or metastatic; SCCHN: squamous cell carcinoma of the head and neck.

NICE National Institute for Health and Care Excellence

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

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2	**Section 3.3. (page 8):** The Committee *"concluded that the [intended for] docetaxel subgroup was the most appropriate data source for this guidance review because it was most relevant to NHS clinical practice"* The all-randomised population from the CheckMate 141 trial is the most appropriate data source for this appraisal and is consistent with the decisions made during the original appraisal. The Company appreciate the Committee's acknowledgement that the CheckMate 141 trial was not powered to detect differences between nivolumab and the individual therapies comprising Investigator's Choice (IC), and thus that the comparison versus docetaxel alone lacks the robustness of using the all-randomised population. Therefore, the Company are disappointed that the Committee consider the intended for docetaxel subgroup to be the most appropriate data source for this guidance review, which is inconsistent with the clinical feedback received during the Committee meeting and contrary to the NICE Technical Team's initial conclusion. Furthermore, this was not an area of uncertainty identified as to be resolved within the CDF Exit process given that the Committee in the original appraisal (TA490) found the results of the CheckMate 141 trial to be relevant to the UK population (Final Appraisal Document [FAD], Section 3.8) and concluded that the model structure, where data from the IC arm were used to inform OS, PFS and TTD for docetaxel, methotrexate and paclitaxel, was appropriate for its decision-making (FAD, Section 3.10). The Company are therefore particularly disappointed that the Committee have come to a different conclusion despite no change in the available data.[4] This decision is perverse. As per the Company response to Technical Engagement, in both the all-randomised population and the intended for docetaxel subgroup, nivolumab was associated with a [redacted], indicated by a [redacted]. However, use of the intended for docetaxel subgroup results in a more conservative estimate of the relative treatment effect for nivolumab. Given the smaller sample size of the intended for docetaxel subgroup, the 95% confidence intervals (CIs) associated with the HR are wider than for the all-randomised population. There is considerable overlap in the 95% CIs of the HRs for the all-randomised population and intended for docetaxel subgroup, which means there is not sufficient evidence to advocate a statistically significant difference between these populations in terms of the treatment effect for OS. These results demonstrate that relative treatment effect in the all-randomised population and intended for docetaxel subgroup can be considered similar, and therefore it is more appropriate to use the all-randomised population. The Company note that patient selection and patterns of therapy choice are likely to affect the apparent relative performance of the individual IC agents in the CheckMate 141 trial. Therefore, analysis of treatment efficacy based on the choice of IC will lead to inherent differences in the studied populations. For example, a higher proportion of patients in the docetaxel arm of the intended for docetaxel subgroup had a baseline ECOG score of 0 than patients in the IC arm of the all-randomised population ([redacted]% versus 19.0%) (see Table 5 of the Company's Technical Engagement Response). Conversely, a lower proportion of patients in the nivolumab arm of the intended for docetaxel subgroup had a baseline ECOG score of 0 than patients in the nivolumab arm of the all-randomised population ([redacted]% versus 20.4%). As compared with the all-randomised population, in which the baseline characteristics across treatment arms are more similar, these differences in the intended for docetaxel subgroup may bias the treatment effect in favour of docetaxel. Furthermore, as discussed later in Comment 4, a higher proportion of patients in the docetaxel arm of the intended for docetaxel subgroup received nivolumab or pembrolizumab as a subsequent therapy as compared with the IC arm as a whole (see Table 2). These differences result in further uncertainty in the outcomes observed in the intended for docetaxel subgroup

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	The Company welcome the Committee's acknowledgement that outcomes in clinical practice (as shown by the Systemic Anti-Cancer Therapy [SACT] data) are reflective of what was seen in the clinical trial for nivolumab. It is important to note that the outcomes for nivolumab in the SACT cohort are more similar to the outcomes for the all-randomised population of CheckMate141 than the intended for docetaxel subgroup, as shown in Figure 2, where the Kaplan-Meier (KM) curve for the intended for docetaxel subgroup diverges from the all-randomised and SACT KM plots at approximately nine months. Therefore, the all-randomised population is more reflective of the patients eligible for nivolumab in NHS practice, which is in agreement with the feedback from the clinical expert consulted in the Company response to Technical Engagement. For the reasons outlined above, it is more appropriate to use the all-randomised population for this appraisal, as it is adequately powered to detect differences between treatment arms and is most reflective of patients in this indication. **Figure 2: Kaplan-Meier plots of overall survival in patients receiving nivolumab in the all-randomised population in CheckMate 141, the intended for docetaxel population of CheckMate 141 and in the SACT cohort**  **Abbreviations:** SACT: Systemic Anti-Cancer Therapy.
3	**Section 3.3 (page 8):** the Cancer Drugs Fund Clinical Lead stated that "*people in the trial (who had an Eastern Cooperative Oncology Group performance status of 0 or 1) would have been fit enough to get docetaxel in NHS clinical practice, and therefore the investigator-choice arm would not be a relevant comparator*." Over the course of this appraisal, the Company have learnt from patients treated with nivolumab within the SACT cohort that the population eligible for nivolumab in clinical practice is broader than those who would otherwise receive docetaxel. As discussed in the Company submission, the SACT cohort included 33 (7%) patients with ECOG performance status 2–3, and 65 (13%) patients with

missing ECOG status, a population more in line with the European Medicines Agency (EMA) licence in this indication, which does not exclude based on performance status, than the CheckMate 141 trial. The clinical expert during the appraisal meeting confirmed that treatment with docetaxel is not considered to confer a survival benefit, and is reserved for symptomatic treatment of patients where the benefits may out-weigh the risks of toxicity. This is in alignment with the clinical feedback noted in the Company response to Technical Engagement that the majority of patients in UK clinical practice in this line of therapy would not receive docetaxel, and instead would receive no active treatment at all (i.e. palliative or best supportive care [BSC]); in many cases, this includes patients who are deemed to be clinically "fit enough" to receive docetaxel. As such, clinical expertise indicates that sufficient fitness does not necessarily mean that docetaxel would be received by these patients in the real-world setting. The Company are disappointed that this input provided during the appraisal from the clinical expert, who routinely treats patients with head and neck cancer in UK clinical practice, was dismissed by the Committee in favour of opinion of the Cancer Drugs Fund clinical lead without rationale.

Therefore, while docetaxel represents the most relevant active comparator for nivolumab, the Company maintain that BSC remains a relevant comparator to this appraisal.

Whilst the arguments outlined above for the relevance of the all-randomised population to inform the comparison of nivolumab versus docetaxel still stand, costs may be overestimated for the patient group as a whole if a large proportion of patients who are "fit enough" to receive docetaxel do not in fact receive it in clinical practice. As such, a scenario has been explored using the efficacy data from the all-randomised population where the acquisition and administration costs for docetaxel have been set to £0 (see Table 1); this results in only marginal increases in the ICER which remains below the willingness-to-pay threshold of £50,000, demonstrating the robustness of the ICER estimates and indicating that nivolumab is a cost-effective use of NHS resources.

Table 1: Cost-effectiveness results for the scenario analysis in which docetaxel acquisition and administration costs are set to zero in the all-randomised population using the full model (Model 1) utility

Assumption	ICER versus docetaxel (£/QALY gained)
Revised Company base case	43,207
No docetaxel acquisition and administration costs	44,597

Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9. Full details of the revised Company base case are presented in Appendix 1.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

4

Section 3.4 (page 8): The ACD states: *"The Cancer Drugs Fund Clinical Lead referred to an amendment update of the clinical protocol for CheckMate 141, which meant that people in the investigator-choice arm could have had nivolumab in the extension phase of the trial. The company did not provide data on how many people switched from investigator choice to nivolumab. It is therefore unclear how a treatment switch would have affected overall survival, which could potentially bias the results against nivolumab."*

The Company welcomes the acknowledgement by the Committee that the use of subsequent treatments or crossover in the IC arm could bias the results against nivolumab, and that use of these data without adjustment could represent a conservative approach.

As presented in Table 2, only [redacted] patients crossed over from the IC arm to nivolumab treatment as of the latest data cut of the CheckMate 141 trial (15th October 2019). However, all of these patients had received docetaxel, which may result in greater uncertainty in the survival estimates for the

intended for docetaxel subgroup relative to the all-randomised population. In addition, several patients in both the all-randomised population and intended for docetaxel subgroup went on to receive subsequent immunotherapy, with a higher proportion of patients in the docetaxel arm of the intended for docetaxel subgroup receiving subsequent nivolumab ([redacted]% versus [redacted]%) and pembrolizumab ([redacted]% versus [redacted]%) compared with the IC arm as a whole. The Company note that receipt of subsequent immunotherapy is not standard clinical practice in the UK, and this may also confound the results.

Table 2: Subsequent therapies received by patients in the nivolumab and Investigator's Choice arms of the all-randomised and intended for docetaxel populations

	All-randomised		Intended for docetaxel	
	Nivolumab (N=240)	IC (N=121)	Nivolumab (N=[redacted])	Docetaxel (N=[redacted])
Cross-over to nivolumab, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any subsequent systemic therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Folic acid analogues	[redacted]	[redacted]	[redacted]	[redacted]
Other monoclonal antibodies [a]	[redacted]	[redacted]	[redacted]	[redacted]
Other immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy [b]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Taxanes	[redacted]	[redacted]	[redacted]	[redacted]

[a] Includes any monoclonal antibody except for nivolumab. [b] Includes both approved and experimental drugs.
Abbreviations: IC: Investigator's Choice.

5

Section 3.5 (page 9): The Committee conclude that there is evidence of nivolumab's benefit for tumours with a PD-L1 score of 1% or higher, but at a lower PD-L1 score the benefit is not clear.

In Section 3.24 (page 21) of the published guidance from the original appraisal, the Committee concluded that the cost-effectiveness results for the PD-L1 subgroups are not suitable for decision making, citing them to be "*subject to uncertainty because of the small patient numbers and because CheckMate-141 was not powered to show a difference between the PD-L1 subgroups*." Therefore, the Company are disappointed that the Committee have altered their conclusion on this topic, despite there being no change in the data available to inform it.

Given this change in Committee conclusion, the Company would like to emphasise that CheckMate 141 was not powered to detect a difference between treatment arms in these subgroups, and that the patient numbers in these subgroups are small: [redacted] patients in the IC arm had confirmed PD-L1 <1%, of whom only [redacted] received docetaxel. As per the study protocol, these subgroups excluded patients in whom PD-L1 status could not be quantified; these patients represent 24% of the all-randomised population. Therefore, as well as the high degree of uncertainty introduced by small patient numbers in these groups, the exclusion of a substantial proportion of the study population from decision making could lead to patients within the NHS not having an effective treatment option available despite evidence in the all-randomised population indicating that they would benefit from nivolumab treatment. Furthermore, the use of these subgroups would provide insufficient evidence

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	to address the decision problem of this appraisal as outlined in the final scope, which was to determine the clinical and cost-effectiveness of nivolumab within its anticipated marketing authorisation for treating recurrent or metastatic (R/M) squamous-cell carcinoma of the head and neck (SCCHN) after platinum-based therapy.[5] Furthermore, from the available data, the overlap between the 95% CI of HRs for nivolumab versus IC in the PD-L1 subgroups and the all-randomised population suggests that there is no statistically significant difference between the populations in terms of the treatment effect for OS (see Figure 4 in the original submission). Despite the 95% CIs overlapping 1 due to the small sample size, the point estimate of the HR indicates a treatment benefit with nivolumab versus IC (HR: 0.74) for the PD-L1 <1% subgroup. The Company welcome the Committee's acknowledgement of the feedback from the clinical expert that suggested PD-L1 score may not be a good predictor of treatment outcomes. As outlined in Comment 1, a significant unmet need irrespective of PD-L1 status remains in patients who would be eligible to receive nivolumab. Given the unmet need and the uncertainty associated with the results from the subgroup analyses based on PD-L1 expression, the all-randomised population should be considered as the patient population within the CDF review.
6	**Section 3.7 (page 11):** The ACD states: "*the extrapolation of overall survival for the [intended for] docetaxel subgroup was uncertain because the assumptions had not been validated and reported with sufficient transparency*" and **Section 3.8 (page 11)** states: "*The most plausible extrapolation method for time to treatment discontinuation for the [intended for] docetaxel subgroup is unknown*". As outlined in Comment 2, the all-randomised population from the CheckMate 141 trial is the most appropriate data source for this appraisal, as it is adequately powered to detect differences between treatment arms and is most reflective of patients in this indication. However, for transparency, a detailed description of the survival analyses explored for the intended for docetaxel subgroup have been presented in Appendix 3 of this response document. Cost-effectiveness results for a variety of plausible extrapolation methods for OS and time to treatment discontinuation (TTD) have been presented in Appendix 2, as requested by the Committee. **Section 3.15 (page 16)**: The ACD notes that *"the committee agreed that the PD-L1 subgroups are of interest within the docetaxel population."* As outlined in Comment 2, the all-randomised population from the CheckMate 141 trial is the most appropriate data source for this appraisal. Additionally, the Committee fail to acknowledge that robust subgroup analyses by PD-L1 expression status within the intended for docetaxel subgroup are not feasible, given the small patient numbers within these groups. As presented in the Company response to Technical Engagement, in the intended for docetaxel subgroup, [redacted] patients had PD-L1 <1% ([redacted] received nivolumab and [redacted] received docetaxel) and [redacted] had PD-L1 ≥1% ([redacted] received nivolumab and [redacted] received docetaxel). Given the high degree of uncertainty introduced by the extremely small numbers of patients in each treatment arm within these subgroups, as well as the risk of selection bias due to broken randomisation, cost effectiveness results suitable for decision-making cannot be generated from these data. In particular, the Company note that, as outlined in Comment 5, the Committee originally identified the small patient numbers and lack of suitable statistical powering in the PD-L1 subgroups to render cost-effectiveness analyses in these subgroups to be unsuitable for decision making. It follows that the analysis of subgroups within these subgroups would be subject to even more uncertainty and are thus similarly inappropriate for decision making.

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7	**Section 3.10 (page 13):** The ACD summarises the Committee's discussion surrounding the duration of treatment benefit of nivolumab. In **Section 3.15 (page 15–16)** the Committee conclude that their preferred approach to modelling includes an assumption of no treatment benefit for nivolumab 5 years after start of treatment and exclusion of a stopping rule. The Company are disappointed that important evidence was omitted from this discussion, which has led to a misunderstanding surrounding the treatment benefit of nivolumab when no stopping rule is applied. As per the Company response to Technical Engagement, inspection of the log cumulative hazards plot for OS (Figure 13 of the original Company submission) clearly shows that towards the end of the observed follow-up period for CheckMate 141 there was a difference between treatment arms in the change in hazards over time, with a reduction in the hazard over time in the nivolumab arm and a relatively constant hazard in the IC arm. It is therefore not appropriate to assume that the hazard in the nivolumab arm becomes equal to the IC arm (i.e. there is no treatment benefit for nivolumab in the long term). This is consistent with the TA490 Committee's preference for the use of piecewise models to extrapolate OS, which are recommended in NICE Technical Support Document (TSD) 14 for modelling datasets in which variable hazards are observed over time. Given the maturity of the data from the CheckMate 141 trial (minimum follow-up of 48.2 months), and the fact that piecewise models were used to extrapolate OS, applying an additional treatment waning assumption in scenarios where no stopping rule is employed is counterintuitive. Accordingly, on Section 3.9 (page 12) of the ACD, it is noted that *"a clinical expert explained that people who are alive 5 years after treatment started are considered 'cured' from the disease."* Applying a treatment waning assumption from 5 years in the absence of a stopping rule is therefore not consistent with clinical reality, given patients alive at 5 years could be assumed to have a similar mortality risk to that of the general population. An updated plot of smoothed hazards over time (in months) is presented in Figure 3 (nivolumab and IC; all-randomised population), where a more appropriate scale has been applied. The plot shows a steeper reduction in hazards being observed in the IC arm compared to the nivolumab arm, and the curves have not yet converged. For the reasons outlined above, it is therefore not appropriate to apply a treatment waning assumption when no stopping rule is employed.

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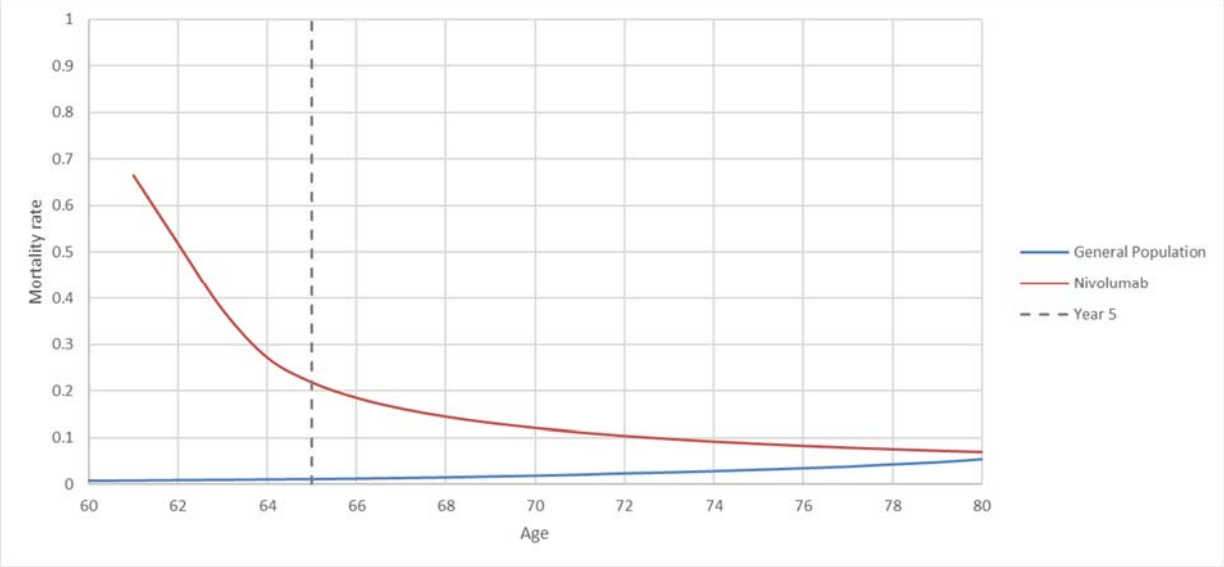
	Figure 3: Smoothed hazards plot for nivolumab and IC overall survival (all-randomised population)  **Abbreviations:** IC: investigator's choice.
8	**Section 3.10 (page 13):** The ACD notes that *"the committee considered that implementing a 2-year stopping rule for nivolumab could affect the relative treatment effect and cause the hazard rates to converge more quickly."* The Company would like to note that, as discussed further in Comment 7 and illustrated in Figure 3, convergence of the overall survival hazard rates for nivolumab IC has been misunderstood by the Committee. A difference between treatment arms in the change in hazards over time was observed towards the end of the follow-up period for CheckMate 141, indicating that hazard rates were not converging. As per the Company response to Technical Engagement, there is accumulating evidence to suggest that treatment with PD-L1 inhibitors, including nivolumab, may facilitate longer term benefit even following treatment discontinuation. In the CheckMate 141 trial, [redacted] of the 13 patients in the nivolumab arm who were alive and in follow-up at the time of the latest data cut [redacted]. In addition, the Company note that implementation of a stopping rule is in line with the recommendation for pembrolizumab in the same indication (where a two year stopping rule was accepted as appropriate by the Committee) and with recommendations for nivolumab in other indications.[2, 6, 7] Given that clinical expert opinion suggests that patients who are in remission following treatment with nivolumab for five years may be considered functionally cured (ACD, Section 3.9), the Company present a revised base case in which a five-year stopping rule is implemented without a treatment

waning assumption (full details of the revised base case are presented in Appendix 1). As discussed in Comment 7, applying a treatment waning assumption from 5 years in the absence of a stopping rule is not consistent with clinical reality, and is not supported by the data from the CheckMate 141 trial. Since patients in remission following treatment with nivolumab at the five year timepoints could be considered functionally cured, these arguments also apply when a 5 year stopping rule is implemented. As shown in Figure 4, in the revised Company base case the mortality rate associated with nivolumab is consistently higher than the mortality rate of the general population. As such, the survival for patients who are alive beyond the 5-year time point (and are considered functionally cured) may be underestimated in the base case, and thus the Company maintain that these base case assumptions are conservative.

Figure 4: Mortality rate for the general population and nivolumab treatment arm of the CheckMate 141 trial over the model horizon in the revised Company base case



Full details of the revised Company base case are presented in Appendix 1. The cost-effectiveness results of the revised company base case including the 5-year stopping rule and no treatment waning are presented in Table 3, including scenario analyses with the PD-L1 subgroups and when no stopping rule has been applied. Despite the fact that long-term survival for patients on nivolumab could be underestimated in the model, these results show that nivolumab is cost effective upon implementation of a five-year stopping rule, demonstrating it to be cost-effective use of NHS resources. Even when no stopping rule is applied, nivolumab remains cost-effective. For reference, the cost-effectiveness results for a variety of scenario combinations of stopping rules, treatment waning assumptions and utility assumptions in these populations are presented in Appendix 2, the majority of which produce ICERs of less than £50,000/QALY.

Table 3: Cost-effectiveness results for the revised Company base case and one scenario combination of a treatment stopping rule and treatment waning assumption

Assumptions	ICER versus docetaxel (£/QALY)
All-randomised population	
5-year stopping rule, no treatment waning ***(Revised Company base case)***	**43,207**

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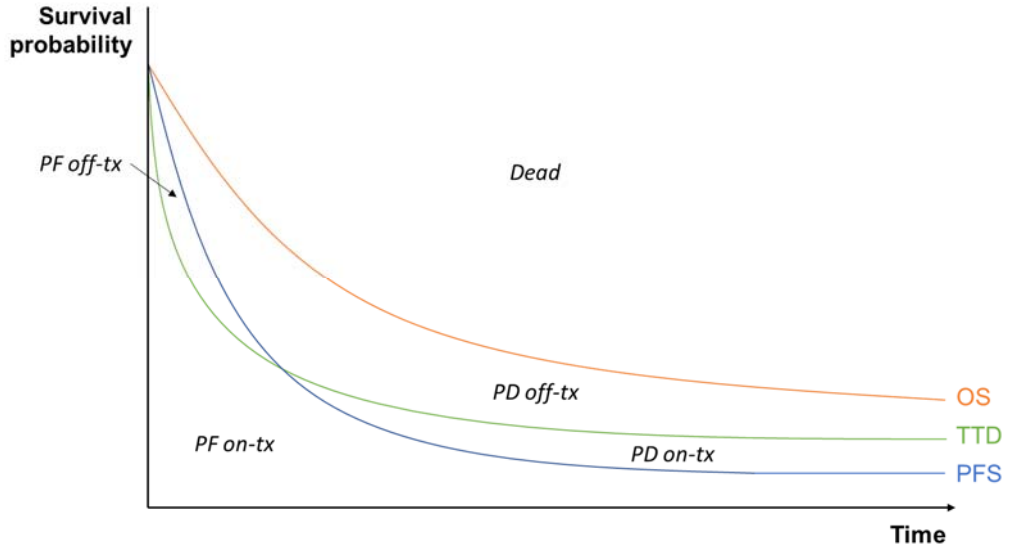
	<table><tr><td>No stopping rule, no treatment waning</td><td>48,442</td></tr><tr><td colspan="2">PD-L1 ≥1%</td></tr><tr><td>5-year stopping rule, no treatment waning</td><td>41,753</td></tr><tr><td>No stopping rule, no treatment waning</td><td>46,121</td></tr><tr><td colspan="2">PD-L1 <1%</td></tr><tr><td>5-year stopping rule, no treatment waning</td><td>48,576</td></tr><tr><td>No stopping rule, no treatment waning</td><td>48,576</td></tr></table> Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9. Full details of the revised Company base case are presented in Appendix 1. **Abbreviations:** ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.
9	**Section 3.11 (page 14):** The ACD notes that *"because no new evidence was presented on quality of life, the committee concluded that the most appropriate approach was to use both treatment-dependent and treatment- independent values in the base-case analysis."* As discussed in response to ERG clarification question B7, no new analysis of utility data was conducted for the latest data cut of the Checkmate 141 trial, given that very few patients in either arm had remained in the trial and completed additional EQ-5D assessments. The Company acknowledge that uncertainty therefore remains in the most appropriate utility values for the model and that these values probably lie between the treatment-dependent and the treatment-independent estimates. As described in the response to Technical Engagement, clinical expert feedback suggested that patients who remain on nivolumab for more than a few months and respond well to treatment are more likely to experience a utility benefit post-progression. The overall response rate (ORR) in CheckMate 141 was greater for nivolumab compared to IC (13.3% versus 5.8%), with a higher proportion of patients in the nivolumab arm achieving a best overall response of either a complete or partial response, as compared to the IC arm.[8] Nivolumab also offers a more durable response compared to IC, with responses maintained beyond 40 weeks for some patients in the nivolumab arm.[8] Therefore, whilst it is recognised that some patients receiving nivolumab may discontinue treatment or progress quickly (and therefore may be expected to have similar utility post-progression to patients who receive IC), the true utility values for the cohort as a whole may lie closer to treatment-dependent than to treatment-independent values. In addition, the mixed model that included progression status and treatment arm (used to derive treatment-specific utility values) was associated with a better statistical fit than the model including progression status alone (treatment-independent utility values). The ERG highlighted in their comments on the Company Technical Engagement response that regression Model 1 and Model 2 (which include a covariate for being off treatment), are associated with even better statistical fit. This approach has previously been accepted by NICE in an oncology indication.[9] Model 2 was considered to lack face validity since it does not include a parameter for progression status. A visual representation of the full model (Model 1), which includes progression status, treatment arm and treatment status, is presented in Figure 5. The derived utilities are presented in Table 4. Whilst this model still predicts a difference in utility between the "PD off-treatment" states for patients receiving nivolumab and IC, this difference is reduced compared to the model used to derive treatment-specific utility values. As such, the Company have updated their preferred base case to include utility values derived from the full model (Model 1), but for all scenarios presented in this response, results in which treatment-dependent and treatment-independent utility values are

presented in Appendix 2 for the Committee's consideration. Estimated utility decrements related to time before death have been excluded in line with the Committee's preferred assumptions.

Figure 5: Visual representation of the full utility model



Abbreviations: OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; TTD: time to treatment discontinuation; tx: treatment.

Table 4: Utility values derived from Model 1 (full model)

	Nivolumab		IC	
	On-treatment	Off-treatment	On-treatment	Off-treatment
PF	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IC: investigator's choice; PD: progressed disease; PF: progression-free.

10

Section 3.13 (page 14): The ACD states that *"based on the evidence provided, the committee concluded that it is uncertain whether nivolumab would extend life by more than 3 months compared with NHS standard care. Therefore, it is currently uncertain if nivolumab meets the end-of-life criteria when compared with docetaxel."* **Section 3.14 (page 15):** The ACD further notes that "*The model estimates for the mean overall-survival benefit are 12 months for the PD-L1 1% and above subgroup, and 6.3 months for the PD-L1 less than 1% subgroup. Because of the uncertainty in the clinical evidence for the PD-L1 less than 1% subgroup, the committee concluded that it is uncertain whether the life-extending criterion was met in that subgroup*."

As discussed further in Comment 2, the Company consider the all-randomised population to be the most relevant for this appraisal. In this population, the data confirm that nivolumab meets the end of life criteria as compared with IC. This conclusion was not identified as an area of uncertainty in the original appraisal process (TA490) where it was accepted by the Committee, and remains valid in the revised Company base case (see Appendix 1) where the estimated survival benefit for nivolumab as compared with IC is 5.4 months.[4] Therefore, the Company are disappointed that the Committee have changed their conclusion despite no change in the source of data informing the end of life criteria decision.

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A detailed description of the survival analyses explored for the intended for docetaxel subgroup has been provided in Appendix 3 of this response document, which should resolve any uncertainty in the extrapolations of OS and TTD. The ACD reports that the mean OS benefit for nivolumab was estimated to be [redacted] months in the intended for docetaxel subgroup. It appears this result has been calculated based on the discounted life years gained (LYG); survival benefit should in fact be based on undiscounted LYG.

Mean survival for nivolumab and the comparator in the docetaxel and PD-L1 <1% subgroups using a range of extrapolation methods for OS are presented in Table 5, alongside the estimated survival benefit for nivolumab. In both subgroups, nivolumab is associated with a survival benefit of considerably more than 3 months versus IC for all OS extrapolations explored. Whilst uncertainty remains in the underlying data for these subgroups given they are derived from small sample sizes, the durability in the survival benefit across a range of extrapolation methods confirm that nivolumab meets the end-of-life criteria within these subgroups.

Table 5: Estimated survival benefit for nivolumab for a variety of extrapolation methods

Extrapolation method for OS [a]	Mean survival (months)		Survival benefit for nivolumab (months)
	Nivolumab	IC/docetaxel	
Intended for docetaxel subgroup			
Piecewise lognormal 96-week cut-off	[redacted]	[redacted]	[redacted]
Piecewise lognormal 48-week cut-off	[redacted]	[redacted]	[redacted]
Fully parametric lognormal	[redacted]	[redacted]	[redacted]
Fully parametric loglogistic	[redacted]	[redacted]	[redacted]
PD-L1 <1% subgroup			
Piecewise lognormal 48-week cut-off	[redacted]	[redacted]	[redacted]
Fully parametric lognormal	[redacted]	[redacted]	[redacted]
Fully parametric loglogistic	[redacted]	[redacted]	[redacted]

[a] In the docetaxel subgroup, the exploratory extrapolation method for OS was applied to both the nivolumab and IC treatment arms. In the PD-L1 <1% subgroup, the exploratory extrapolation method for OS was applied to the nivolumab treatment arm only, given that [redacted]

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Appendices

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Appendix 1 – Revised Company base case results

The inputs implemented in the revised Company base case are as follows:

- Population: all-randomised
- Stopping rule: 5 years
- Treatment waning: None
- OS extrapolation: 96-week lognormal for nivolumab arm; 96-week lognormal for IC arm
- PFS extrapolation: generalised gamma for nivolumab arm; generalised gamma for IC arm
- TTD extrapolation: 2-spline normal for nivolumab arm; [redacted] for IC arm
- Utility values: full model (Model 1)

The cost-effectiveness results of the revised Company base case are presented in Table 1.

Table 1: Revised Company base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Docetaxel	10,561	0.67	0.35	[redacted]	0.65	[redacted]	£43,207

Note that time-to-death utility decrements have not been applied.
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

Appendix 2 – Additional cost-effectiveness results in the all-randomised population and PD-L1 subgroups

Table 2: Cost-effectiveness results for various combinations of a treatment stopping rule, treatment waning assumption and utility assumption

Assumptions	ICER versus docetaxel (£/QALY)		
	Full model (Model 1) *Base case assumption*	Treatment-specific utility	Treatment-independent utility
All-randomised (base case) population			
2-year stopping rule No treatment waning *(Company base case at TE)*	36,802	35,357	41,557
2-year stopping rule 3-year treatment waning	50,336	49,168	60,529

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2-year stopping rule 5-year treatment waning	43,601	42,222	50,748
5-year stopping rule 5-year treatment waning	51,305	49,682	59,714
5-year stopping rule **No treatment waning** ***(Revised Company base case)***	**43,207**	**41,511**	**48,789**
No stopping rule No treatment waning	48,442	46,540	54,700
PD-L1 ≥1%			
2-year stopping rule No treatment waning	36,039	34,718	38,980
2-year stopping rule 3-year treatment waning	48,291	47,325	54,386
2-year stopping rule 5-year treatment waning	42,179	40,958	46,493
5-year stopping rule 5-year treatment waning	48,965	47,548	53,972
5-year stopping rule No treatment waning	41,753	40,222	45,160
No stopping rule No treatment waning	46,121	44,430	49,885
PD-L1 <1%			
2-year stopping rule No treatment waning	44,771	43,181	54,041
2-year stopping rule 3-year treatment waning	56,851	54,990	72,804
2-year stopping rule 5-year treatment waning	50,048	48,319	61,947
5-year stopping rule 5-year treatment waning	54,339	52,462	67,258
5-year stopping rule No treatment waning	48,576	46,851	58,634
No stopping rule No treatment waning	48,576	46,851	58,634

Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; TE: Technical Engagement.

Table 3: Cost-effectiveness results for the all-randomised (base case) population using alternative OS and TTD extrapolations

Scenario	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on ICER (£)
Revised base case	**OS:** Piecewise lognormal 96-week cut-off for both nivolumab and docetaxel **TTD:** 2-spline normal for nivolumab, [redacted]	43,207	-
Alternative OS assumption	Piecewise lognormal 48-week cut-off for both nivolumab and IC	46,286	+3,079
Alternative OS assumption	Fully parametric lognormal for both nivolumab and IC	47,314	+4,107
Alternative OS assumption	Fully parametric loglogistic for both nivolumab and IC	45,068	+1,861
Alternative TTD assumption	Generalised gamma for both nivolumab and IC	42,436	−771

Abbreviations: K-M: Kaplan-Meier; IC: Investigator's choice; ICER: incremental cost effectiveness ratio; OS: overall survival; TTD: time to treatment discontinuation.

Appendix 3 – Survival assumptions and cost-effectiveness results for the intended for docetaxel subgroup

Overall survival

As per the Committee's preferred approach in TA490 and in alignment with the additional analysis presented by the Company at Technical Engagement, the piecewise method was used to extrapolate OS for the intended for docetaxel subgroup. The distributions that were explored were the exponential distribution, as recommended in Bagust and Beale (2014), and also the lognormal distribution, which represented the Committee's preferred extrapolation in TA490.[1] To inform the choice of timepoint to extrapolate from, the log-cumulative hazards plot was inspected (see Figure 1). As for the all-randomised population, there is a noticeable change in hazard from Week 20 in both treatment arms. For IC (docetaxel), the hazard appears to be relatively constant over time from Week 20 onwards, whereas for nivolumab there is a trend towards a reduction in the hazard over time, which would favour the use of the lognormal distribution.

Visual inspection of these piecewise extrapolations compared to the observed trial data showed that the exponential distributions produced a poorer fit than the lognormal distributions (see Figure 2). When looking only at the lognormal distribution, the visual fit was fairly similar across the timepoints explored, with both providing a reasonable fit to the observed trial data. Only the piecewise models using the lognormal distribution were therefore considered for the intended for docetaxel subgroup, with preference given to the Week 96 timepoint in order to maximise the use of observed trial data.

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Figure 1: Log cumulative hazard plot for overall survival in the intended for docetaxel subgroup

Figure 2: Long-term OS extrapolation using piecewise models for nivolumab and IC (intended for docetaxel subgroup)

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

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In addition to the piecewise models, fully parametric extrapolations of the observed data were also explored. AIC and BIC values for each fully parametric survival model are presented in Table 4, and the long-term extrapolations of OS using each model are presented in Figure 3 and Figure 4, for nivolumab and docetaxel, respectively. As per the all-randomised population, the fully parametric lognormal curve was associated with the best statistical fit to both the nivolumab and docetaxel arms, and provided a reasonable visual fit to the observed data from the intended for docetaxel subgroup. The loglogistic curve, which is also associated with decreasing hazards over time, also provided a reasonable fit to the observed data and was one of the better fitting non-spline curves in terms of AIC and BIC. Long-term extrapolations using the fully parametric lognormal and loglogistic models are presented in Figure 5, alongside the lognormal piecewise models.

Based on the above, the fully parametric models are still considered to provide plausible extrapolations of OS with nivolumab and docetaxel and therefore have been explored in scenario analyses, alongside the 96-week piecewise model that represented the base case approach for the all-randomised population.

Table 4: Summary of goodness-of-fit data for overall survival – intended for docetaxel subgroup

Distribution	Nivolumab		Docetaxel	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each arm is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

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Figure 3: Long-term OS extrapolation of parametric and piecewise models for nivolumab (intended for docetaxel subgroup)

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

Figure 4: Long-term OS extrapolation of parametric and piecewise models for docetaxel (intended for docetaxel subgroup)

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

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Figure 5: Long-term OS extrapolation using fully parametric lognormal and loglogistic models, and piecewise models for nivolumab and docetaxel (intended for docetaxel subgroup)

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

Progression-free survival

A variety of parametric and spline models were explored to extrapolate PFS for the intended for docetaxel subgroup. AIC and BIC values for each survival model are presented in Table 5, and the long-term extrapolations of PFS using each model are presented in Figure 6 and Figure 7 for nivolumab and docetaxel, respectively.

Of those explored, the spline models provided a better statistical fit for nivolumab than the standard parametric models, but the best-fitting curves often produced logical inconsistencies when compared to the preferred extrapolation for OS (with or without the treatment waning effect applied), whereby PFS was higher than OS. Excluding the spline models, the lognormal and loglogistic models provided the best statistical fit for docetaxel but were associated with a poor statistical and visual fit to the observed data for nivolumab in the long term. The generalised gamma model provided the best statistical fit for nivolumab and good visual fit to both arms was therefore explored for alignment with the all-randomised population (Figure 8).

Table 5: Summary of goodness-of-fit data for progression-free survival – intended for docetaxel subgroup

Distribution	Nivolumab		Docetaxel	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]

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Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each arm is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 6: Long-term PFS extrapolation of parametric models for nivolumab (intended for docetaxel subgroup)

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

Figure 7: Long-term PFS extrapolation of parametric models for docetaxel (intended for docetaxel subgroup)

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

Figure 8: Long-term PFS extrapolation of most plausible models for nivolumab and docetaxel (intended for docetaxel subgroup)

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

Time to treatment discontinuation

As for PFS, a variety of parametric and spline models were explored to extrapolate TTD for the intended for docetaxel subgroup. AIC and BIC values for each survival model are presented in Table 6, and the long-term extrapolations of TTD using each model are presented in Figure 9 and Figure 10 for nivolumab and docetaxel, respectively.

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[redacted]. For nivolumab, as per the all-randomised population, the spline models were associated with the best statistical fit. Of these, the 2 spline normal model provided the best statistical fit and a reasonable visual fit to the observed data. Additionally, compared with mean PFS, mean TTD predicted by the model [redacted]. The 2 spline normal model was therefore considered to be most plausible extrapolation of TTD. However, in alignment with the ERG preferences for the all-randomised population, the generalised gamma model was also explored for extrapolation of the nivolumab and docetaxel arms (Figure 11).

Table 6: Summary of goodness-of-fit data for time to treatment discontinuation – intended for docetaxel subgroup

Distribution	Nivolumab		Docetaxel	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each arm is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

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Figure 9: Long-term TTD extrapolation of parametric models for nivolumab (intended for docetaxel subgroup)

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

Figure 10: Long-term TTD extrapolation of parametric models for docetaxel (intended for docetaxel subgroup)

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

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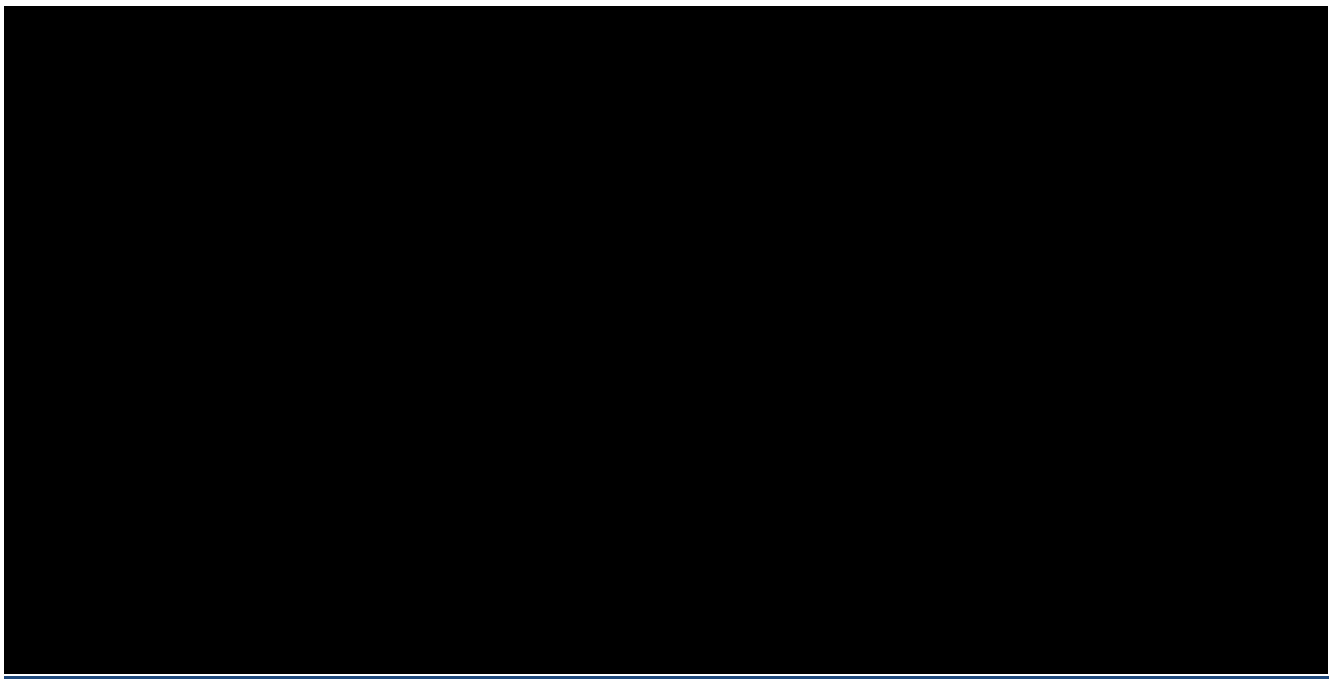
Figure 11: Long-term TTD extrapolation of most plausible models for nivolumab and IC (intended for docetaxel subgroup)



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

Cost-effectiveness data in the intended for docetaxel subgroup

Table 7: Cost-effectiveness results for the intended for docetaxel subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Intended for docetaxel subgroup [a]							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Docetaxel	11,213	0.85	0.44	[redacted]	0.56	[redacted]	51,342
Scenario: intended for docetaxel subgroup with treatment-specific utility							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Docetaxel	11,213	0.85	0.46	[redacted]	0.56	[redacted]	51,897
Scenario: intended for docetaxel subgroup with treatment-independent utility							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Docetaxel	11,213	0.85	0.52	[redacted]	0.56	[redacted]	62,381

Note that time-to-death utility decrements have not been applied in these scenarios.
[a] This subgroup analysis was run using assumptions matching those employed in the revised Company base case, including utilities derived from the full model (Model 1). See Appendix 1 for full details.
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

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Table 8: Cost-effectiveness results for the intended for docetaxel subgroup for alternative OS and TTD extrapolations

Scenario in the intended for docetaxel subgroup	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on ICER (£)
Revised base case assumptions [a]	**OS:** Piecewise lognormal 96-week cut-off for both nivolumab and docetaxel **TTD:** 2-spline normal for nivolumab, [redacted]	51,342	-
Alternative OS assumption	Piecewise lognormal 48-week cut-off for both nivolumab and docetaxel	54,563	+3,221
Alternative OS assumption	Fully parametric lognormal for both nivolumab and docetaxel	54,874	+3,532
Alternative OS assumption	Fully parametric loglogistic for both nivolumab and docetaxel	50,800	−542
Alternative TTD assumption	Generalised gamma for both nivolumab and docetaxel	49,514	−1,828
Revised base case assumptions using TS and TI	**OS:** Piecewise lognormal 96-week cut-off for both nivolumab and docetaxel **TTD:** 2-spline normal for nivolumab, [redacted]	TS: 51,897 TI: 62,381	-
Alternative OS assumption	Piecewise lognormal 48-week cut-off for both nivolumab and docetaxel	TS: 55,322 TI: 66,898	TS: +3,425 TI: +4,517
Alternative OS assumption	Fully parametric lognormal for both nivolumab and docetaxel	TS: 55,671 TI: 67,429	TS: +3,774 TI: +5,048
Alternative OS assumption	Fully parametric loglogistic for both nivolumab and docetaxel	TS: 51,215 TI: 61,880	TS: −682 TI: −501
Alternative TTD assumption	Generalised gamma for both nivolumab and docetaxel	TS: 51,815 TI: 62,283	TS: −82 TI: −98

Note that time-to-death utility decrements have not been applied in these scenarios.
[a] This subgroup analysis was run using assumptions matching those employed in the revised Company base case, including utilities derived from the full model (Model 1). See Appendix 1 for full details.
Abbreviations: FM: full model; ICER: incremental cost effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; TI: treatment-independent utility; TS: treatment-specific utility; TTD: time to treatment discontinuation.

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Appraisal Consultation Document Response – Appendix 2

The tables in this document show the cost-effectiveness results presented in the ACD response document and appendix [redacted]

Main Response Document

Table 1: Cost-effectiveness results for the scenario analysis in which docetaxel acquisition and administration costs are set to zero in the all-randomised population using the full model (Model 1) utility

Assumption	ICER versus docetaxel (£/QALY gained)
Revised Company base case	40,069
No docetaxel acquisition and administration costs	41,458

Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9. Full details of the revised Company base case are presented in the Appendix document.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

Table 3: Cost-effectiveness results for the revised Company base case and one scenario combination of a treatment stopping rule and treatment waning assumption

Assumptions	ICER versus docetaxel (£/QALY)
All-randomised population	
5-year stopping rule, no treatment waning *(Revised Company base case)*	**40,069**
No stopping rule, no treatment waning	44,922
PD-L1 ≥1%	
5-year stopping rule, no treatment waning	38,822
No stopping rule, no treatment waning	42,872
PD-L1 <1%	
5-year stopping rule, no treatment waning	44,890
No stopping rule, no treatment waning	44,890

Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9. Full details of the revised Company base case are presented in the Appendix document.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

Appendix Document

Table 1: Revised Company base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Docetaxel	10,561	0.67	0.35	[redacted]	0.65	[redacted]	40,069

Note that time-to-death utility decrements have not been applied.
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

Table 2: Cost-effectiveness results for various combinations of a treatment stopping rule, treatment waning assumption and utility assumption

Assumptions	ICER versus docetaxel (£/QALY)		
	Full model (Model 1) *Base case*	Treatment-specific utility	Treatment-independent utility
All-randomised (base case) population			
2-year stopping rule No treatment waning *(Company base case at TE)*	34,130	32,790	38,539
2-year stopping rule 3-year treatment waning	46,579	45,498	56,012
2-year stopping rule 5-year treatment waning	40,387	39,109	47,006
5-year stopping rule 5-year treatment waning	47,530	46,027	55,320
5-year stopping rule **No treatment waning** ***(Revised Company base case)***	**40,069**	**38,496**	**45,245**
No stopping rule No treatment waning	44,922	43,159	50,726
PD-L1 ≥1%			
2-year stopping rule No treatment waning	33,524	32,295	36,260
2-year stopping rule 3-year treatment waning	44,829	43,932	50,487
2-year stopping rule 5-year treatment waning	39,191	38,057	43,200
5-year stopping rule 5-year treatment waning	45,484	44,167	50,135
5-year stopping rule No treatment waning	38,822	37,399	41,990
No stopping rule No treatment waning	42,872	41,301	46,371
PD-L1 <1%			
2-year stopping rule No treatment waning	41,362	39,893	49,926
2-year stopping rule 3-year treatment waning	52,444	50,727	67,160

2-year stopping rule 5-year treatment waning	46,205	44,608	57,190
5-year stopping rule 5-year treatment waning	50,183	48,450	62,115
5-year stopping rule No treatment waning	44,890	43,296	54,185
No stopping rule No treatment waning	44,890	43,296	54,185

Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; TE: Technical Engagement.

Table 3: Cost-effectiveness results for the all-randomised (base case) population using alternative OS and TTD extrapolations

Scenario	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on ICER (£)
Revised base case	**OS:** Piecewise lognormal 96-week cut-off for both nivolumab and docetaxel **TTD:** 2-spline normal for nivolumab, [redacted]	**40,069**	-
Alternative OS assumption	Piecewise lognormal 48-week cut-off for both nivolumab and IC	42,906	+2,837
Alternative OS assumption	Fully parametric lognormal for both nivolumab and IC	43,853	+3,784
Alternative OS assumption	Fully parametric loglogistic for both nivolumab and IC	41,781	+1,712
Alternative TTD assumption	Generalised gamma for both nivolumab and IC	39,362	−707

Abbreviations: K-M: Kaplan-Meier; IC: Investigator's choice; ICER: incremental cost effectiveness ratio; OS: overall survival; TTD: time to treatment discontinuation.

Table 7: Cost-effectiveness results for the intended for docetaxel subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Intended for docetaxel subgroup [a]							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	0.56	[redacted]	£47,577
Scenario: intended for docetaxel subgroup with treatment-specific utility							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	0.56	[redacted]	£48,091
Scenario: intended for docetaxel subgroup with treatment-independent utility							
Nivolumab	[redacted]	[redacted]	[redacted]				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	0.56	[redacted]	£57,807

Note that time-to-death utility decrements have not been applied in these scenarios.
[a] This subgroup analysis was run using assumptions matching those employed in the revised Company base case, including utilities derived from the full model (Model 1). See the Appendix document for full details.
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

Table 8: Cost-effectiveness results for the intended for docetaxel subgroup for alternative OS and TTD extrapolations

Scenario in the intended for docetaxel subgroup	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on ICER (£)
Revised base case assumptions [a]	**OS:** Piecewise lognormal 96-week cut-off for both nivolumab and docetaxel **TTD:** 2-spline normal for nivolumab, [redacted]	47,577	-
Alternative OS assumption	Piecewise lognormal 48-week cut-off for both nivolumab and docetaxel	50,547	+2,970
Alternative OS assumption	Fully parametric lognormal for both nivolumab and docetaxel	50,834	+3,257
Alternative OS assumption	Fully parametric loglogistic for both nivolumab and docetaxel	47,077	−500
Alternative TTD assumption	Generalised gamma for both nivolumab and docetaxel	45,893	−1,684
Revised base case assumptions using TS and TI	**OS:** Piecewise lognormal 96-week cut-off for both nivolumab and docetaxel **TTD:** 2-spline normal for nivolumab, [redacted]	TS: 48,091 TI: 57,807	TS: +514 TI: +10,230
Alternative OS assumption	Piecewise lognormal 48-week cut-off for both nivolumab and docetaxel	TS: 51,250 TI: 61,975	TS: +3,673 TI: +14,398
Alternative OS assumption	Fully parametric lognormal for both nivolumab and docetaxel	TS: 51,572 TI: 62,465	TS: +3,995 TI: +14,888
Alternative OS assumption	Fully parametric loglogistic for both nivolumab and docetaxel	TS: 47,461 TI: 57,344	TS: −116 TI: +9,767
Alternative TTD assumption	Generalised gamma for both nivolumab and docetaxel	TS: 48,026 TI: 57,728	TS: +449 TI: +10,151

Note that time-to-death utility decrements have not been applied in these scenarios.
[a] This subgroup analysis was run using assumptions matching those employed in the revised Company base case, including utilities derived from the full model (Model 1). See the Appendix Document for full details.
Abbreviations: FM: full model; ICER: incremental cost effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; TI: treatment-independent utility; TS: treatment-specific utility; TTD: time to treatment discontinuation

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Consultation on the appraisal consultation document – deadline for comments 5:00pm on 28 January 2021 via NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Head And Neck Cancer UK (HANCUK)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Insofar as the comments from HANCUK and the oral evidence presented at Committee are concerned, the report presents a fair and balanced summary.
2	
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Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[**Andrew Sykes**]

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	I am very disappointed in the decision to de-list Nivolumab for the treatment of patients with recurrent/metastatic head and neck cancer previously treated within 6 month with platinum base chemotherapy. Nivolumab is a significant improvement in our ability to treat these patients over the existing treatment options. It is a well-tolerated treatment that extends survival in a significant number of patients and is the first treatment that has shown a survival benefit for patients who have progressed after platinum containing therapy. I think the committee has failed to understand 2 important points that support the use of Nivolumab which I will discuss below.
1	**The committee agreed that most people who will be eligible for immunotherapy in later lines of treatment will have a PD-L1 score of less than 1** In paragraph 3.2 of the consultation appraisal document it is discussed that Cetuximab therapy and Pembrolizumab therapy have changed the treatment paradigm. In particular it is asserted that because Pembrolizumab is used earlier in the treatment pathway it will lead to the use of Nivolumab mainly in patients who are PD-L1 <1% ("The committee agreed that most people who will be eligible for immunotherapy in later lines of treatment will have a PD-L1 score of less than 1"). This is factually incorrect. In my practice (one of the largest, if not the largest, in the UK) 40% of patients are eligible for Nivolumab when they have relapsed within 6 months of chemo-radiotherapy with platinum. These patients are not exclusively PD-L1 <1%, in fact we know that the large majority of them are PD-L1 >1%. It is therefore incorrect to say that Nivolumab would be reserved largely for the treatment of PD-L1 <1% patients. Nivolumab would be used for patients with all levels of PD-L1, but the great majority of them would be >1%.
2	**The comparison with the docetaxel subgroup from CheckMate 141 is most relevant to UK clinical practice.** The comparison with Docetaxel is discussed in paragraphs 3.3 and 3.4, where it is stated that "the clinical benefit of Nivolumab compared to Docetaxel alone is not clear". I believe that the committee is mistaken in trying to compare Nivolumab with the Docetaxel subgroup. Docetaxel is an intensive regime with significant toxicity. In the real world outside the trial setting, very few patients with recurrent/metastatic head and neck cancer are able to tolerate treatment with Docetaxel. Prior to Nivolumab my centre would treat <5 patients per year with Docetaxel. Patients who were treated would rarely receive beyond 3 cycles because of the significant haematological toxicity associated with the drug. Patients over the age of 70 were especially likely to experience toxicity, limiting its use to younger patients. In comparison we treat 30+ new patents with Nivolumab which is significantly better tolerated. Especially by patients in the over 70 age group. Patients have to be ECOG PS 0-1 to receive Nivolumab and it is noted that there was no significant difference between PS scores in the 3 different IC treatment groups. However while ECOG PS is very useful in many respects it can hide significant differences in ability to tolerate treatment. Not all PS 1 patients are the same (For example PS hides the effect of age eg. a PS 1 80yr old will not tolerate Docetaxel while a PS 1 60yr old might). Unfortunately it is well recognised that clinical trials are not representative of patients in the real world. What is especially impressive however is how well the results of treating patients with Nivolumab do translate to the clinic. Both the CDF follow up data and my own audit show that the results in the real world match those of CheckMate 141. In reality, the real world comparator is best supportive care, but in the absence of this in a clinical trial the ITT group should be used rather than the Docetaxel subgroup.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bristol Myers Squibb Pharmaceuticals Ltd	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None	
Name of commentator person completing form:	[redacted]	

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.	ERG critique
	Bristol-Myers Squibb (BMS) Pharmaceuticals Limited would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for nivolumab for treating recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) after platinum-based chemotherapy [ID1585] (CDF Review of TA490). We are highly disappointed that the Appraisal Committee has ignored the clinical expert feedback 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. The unmet need in these patients has been heightened during the ongoing COVID-19 pandemic: in the UK between March and May 2020, urgent referrals	

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	for people with a suspicion of head and neck cancer dropped by 59%, which is projected to significantly impact 5-year survival time in these patients.[1] We believe that the basis for this preliminary decision relies on the Committee reaching several conclusions directly in contradiction to those reached in the original appraisal (TA490) despite the data informing these issues remaining unchanged. In response to the ACD, BMS have presented a revised economic base case to address the Committee's concerns regarding the suitability of implementing a 2-year stopping rule for nivolumab treatment. This revised base case is associated with an incremental cost-effectiveness ratio (ICER) below the willingness-to-pay threshold of £50,000 for medicines which reach the end-of-life criteria and thus demonstrates nivolumab to be a cost-effective use of NHS resources. 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 R/M SCCHN after platinum-based chemotherapy in UK clinical practice.	
1	**Section 3.2 (page 6):** The Committee note that "*both [cetuximab combination therapy and pembrolizumab monotherapy] are used earlier in the treatment pathway than nivolumab*" and that *"pembrolizumab is recommended for untreated metastatic or unresectable recurrent SCCHN in adults whose tumours express PD-L1 with a combined positive score of 1 or more. But in NHS clinical practice, people would only have immunotherapy once during the treatment pathway. Therefore, the committee agreed that most people who will be eligible for immunotherapy in later lines of treatment will have tumours that have a PD-L1 score of less than 1."* Similar arguments are reported in Section 3.5 (page 9). The Committee have mis-represented the target population for this submission in the ACD. The Company maintain that there remains an unmet need in the indication of relevance for this submission for patients irrespective of programmed death ligand 1 (PD-L1) status. The indication of relevance for this submission is: "*nivolumab monotherapy for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) in adults progressing on or after platinum-based therapy*". As shown in Figure 1, this population includes	The ERG would concur with the company that the relevant population appears to be the subgroups of the original population that are: 1) PD-L1 <1%, not arising in the oral cavity and untreated at the R/M stage 2) Any PD-L1 status and progressed within 6 months of early/locally advanced stage

	patients who progress following platinum-based therapy in the recurrent or metastatic (R/M) setting and patients who progress following platinum-based therapy as part of an earlier-stage intervention for the treatment of locally advanced disease. Cetuximab in combination with platinum-based chemotherapy is recommended for treating recurrent or metastatic squamous cell cancer of the head and neck in cancers that started in the oral cavity, and pembrolizumab is recommended for untreated metastatic or unresectable recurrent SCCHN for patients whose tumours express PD-L1 with a combined positive score (CPS) of 1 or more (as shown in Figure 1).[2, 3] As patients who have progressed following platinum-based therapy in the locally-advanced setting would be eligible for nivolumab first line in the R/M setting, the conclusion of the Committee that cetuximab and pembrolizumab are used earlier in the treatment pathway than nivolumab is incorrect, with all three eligible for first-line use in the R/M setting for some patients. The Company agree that patients who receive pembrolizumab in the R/M setting would not receive nivolumab in a later line of treatment. However, nivolumab is available to patients who have progressed within 6 months of receiving platinum-based therapy in the locally advanced disease setting. For these patients, there may be a choice between receiving pembrolizumab in those who have PD-L1 >1%, cetuximab in those whose disease began in the oral cavity, or nivolumab in patients regardless of their PD-L1 status or disease origin location. Patients that progressed within 6 months of receiving platinum-based therapy in the locally advanced disease setting constitute a considerable proportion of patients eligible for nivolumab in clinical practice, with a clinical expert consulted as part of this response estimating this proportion to be 40% of patients. Nivolumab would also remain the only immunotherapy option for patients who are PD-L1 <1%, or whose PD-L1 status cannot be determined. This includes patients for whom immediate treatment initiation is clinically necessary and thus PD-L1 status would not be ascertained prior to treatment commencement. In addition to the acknowledgement by the clinical expert in the ACD that the availability of PD-L1 testing varies across the NHS in England (Section 3.5, page 9), a clinical expert consulted as part of this response highlighted that obtaining the results of a PD-L1 test is highly variable between multidisciplinary teams and may take several weeks in UK clinical practice.	

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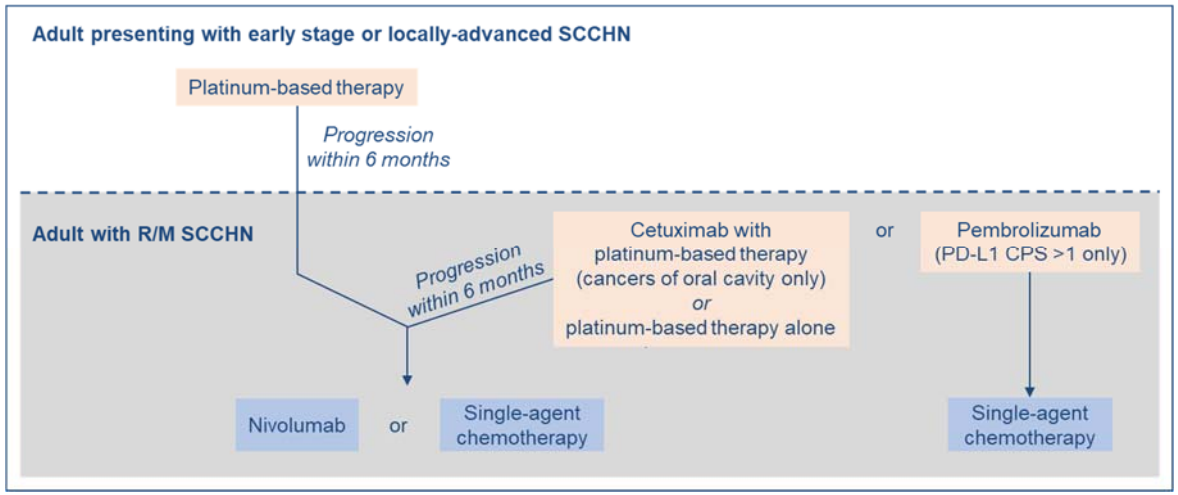
	Therefore, the Company consider nivolumab would address a significant area of unmet need in UK clinical practice despite the introduction of cetuximab and pembrolizumab and regardless of PD-L1 status. **Figure 1: Clinical care pathway for adults with R/M SCCHN who have progressed after platinum-based therapy**  Patients with SCCHN may receive platinum-based therapy first-line in the R/M setting or as part of an earlier-stage intervention for the treatment of locally advanced disease. In the R/M setting, patients with a combined positive score of 1 or more may receive pembrolizumab first-line and patients with cancer of the oral cavity may receive cetuximab. Patients who may be considered eligible for treatment with nivolumab under the anticipated indication for SCCHN are expected to have progressed within 6 months of having received platinum-based therapy, but may have received this therapy in either setting. **Abbreviations:** CPS: combined positive score; R/M: recurrent or metastatic; SCCHN: squamous cell carcinoma of the head and neck.	
2	**Section 3.3. (page 8):** The Committee *"concluded that the [intended for] docetaxel subgroup was the most appropriate data source for this guidance review because it was most relevant to NHS clinical practice"*	The ERG continue to assert that the docetaxel subgroup is the most appropriate data source to inform the comparison between nivolumab and docetaxel in those

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	The all-randomised population from the CheckMate 141 trial is the most appropriate data source for this appraisal and is consistent with the decisions made during the original appraisal. The Company appreciate the Committee's acknowledgement that the CheckMate 141 trial was not powered to detect differences between nivolumab and the individual therapies comprising Investigator's Choice (IC), and thus that the comparison versus docetaxel alone lacks the robustness of using the all-randomised population. Therefore, the Company are disappointed that the Committee consider the intended for docetaxel subgroup to be the most appropriate data source for this guidance review, which is inconsistent with the clinical feedback received during the Committee meeting and contrary to the NICE Technical Team's initial conclusion. Furthermore, this was not an area of uncertainty identified as to be resolved within the CDF Exit process given that the Committee in the original appraisal (TA490) found the results of the CheckMate 141 trial to be relevant to the UK population (Final Appraisal Document [FAD], Section 3.8) and concluded that the model structure, where data from the IC arm were used to inform OS, PFS and TTD for docetaxel, methotrexate and paclitaxel, was appropriate for its decision-making (FAD, Section 3.10). The Company are therefore particularly disappointed that the Committee have come to a different conclusion despite no change in the available data.[4] This decision is perverse. As per the Company response to Technical Engagement, in both the all-randomised population and the intended for docetaxel subgroup, nivolumab was associated with a [redacted], indicated by a [redacted]. However, use of the intended for docetaxel subgroup results in a more conservative estimate of the relative treatment effect for nivolumab. Given the smaller sample size of the intended for docetaxel subgroup, the 95% confidence intervals (CIs) associated with the HR are wider than for the all-randomised population. There is considerable overlap in the 95% CIs of the HRs for the all-randomised population and intended for docetaxel subgroup, which means there is not sufficient evidence to advocate a statistically significant difference between these populations in terms of the treatment effect for OS. These results demonstrate that relative treatment effect in the all-randomised population and intended for docetaxel subgroup can be considered similar, and therefore it is more appropriate to use the all-randomised population. The Company note that patient selection and patterns of therapy choice are likely to affect the apparent relative performance of the individual IC agents in the CheckMate 141 trial. Therefore, analysis of treatment efficacy based on the choice of IC will lead to inherent differences in the	who, without nivolumab, would receive docetaxel i.e. where docetaxel is standard of care. The observation that the relative treatment effect is similar between the all-randomised and the docetaxel subgroup is insufficient to overturn this conclusion: indeed, the implication would be that trial data in the relevant population should be rejected in favour of that in a wider population in order to increase sample size i.e. to trade reduced risk of bias for precision. Of course, ultimately it is the judgment of the committee that is paramount in valuing the trade-off between risk of bias and precision. The ERG also recognise the differences in observed baseline characteristics between arms. Given that there was randomisation, this must have occurred by chance, as would differences in unobserved characteristics. Therefore, the difference in all effect modifiers between arms in the all-randomisation relative to the docetaxel subgroup cannot be known. The ERG also recognises that a comparison with the SACT data can be informative of the outcome with nivolumab, but it is not very helpful in informing the size of the relative treatment effect between nivolumab and docetaxel.

	studied populations. For example, a higher proportion of patients in the docetaxel arm of the intended for docetaxel subgroup had a baseline ECOG score of 0 than patients in the IC arm of the all-randomised population ([redacted]% versus 19.0%) (see Table 5 of the Company's Technical Engagement Response). Conversely, a lower proportion of patients in the nivolumab arm of the intended for docetaxel subgroup had a baseline ECOG score of 0 than patients in the nivolumab arm of the all-randomised population ([redacted]% versus 20.4%). As compared with the all-randomised population, in which the baseline characteristics across treatment arms are more similar, these differences in the intended for docetaxel subgroup may bias the treatment effect in favour of docetaxel. Furthermore, as discussed later in Comment 4, a higher proportion of patients in the docetaxel arm of the intended for docetaxel subgroup received nivolumab or pembrolizumab as a subsequent therapy as compared with the IC arm as a whole (see Table 2). These differences result in further uncertainty in the outcomes observed in the intended for docetaxel subgroup The Company welcome the Committee's acknowledgement that outcomes in clinical practice (as shown by the Systemic Anti-Cancer Therapy [SACT] data) are reflective of what was seen in the clinical trial for nivolumab. It is important to note that the outcomes for nivolumab in the SACT cohort are more similar to the outcomes for the all-randomised population of CheckMate141 than the intended for docetaxel subgroup, as shown in Figure 2, where the Kaplan-Meier (KM) curve for the intended for docetaxel subgroup diverges from the all-randomised and SACT KM plots at approximately nine months. Therefore, the all-randomised population is more reflective of the patients eligible for nivolumab in NHS practice, which is in agreement with the feedback from the clinical expert consulted in the Company response to Technical Engagement. For the reasons outlined above, it is more appropriate to use the all-randomised population for this appraisal, as it is adequately powered to detect differences between treatment arms and is most reflective of patients in this indication.	

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Figure 2: Kaplan-Meier plots of overall survival in patients receiving nivolumab in the all-randomised population in CheckMate 141, the intended for docetaxel population of CheckMate 141 and in the SACT cohort

Abbreviations: SACT: Systemic Anti-Cancer Therapy.

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3	**Section 3.3 (page 8):** the Cancer Drugs Fund Clinical Lead stated that "*people in the trial (who had an Eastern Cooperative Oncology Group performance status of 0 or 1) would have been fit enough to get docetaxel in NHS clinical practice, and therefore the investigator-choice arm would not be a relevant comparator*." Over the course of this appraisal, the Company have learnt from patients treated with nivolumab within the SACT cohort that the population eligible for nivolumab in clinical practice is broader than those who would otherwise receive docetaxel. As discussed in the Company submission, the SACT cohort included 33 (7%) patients with ECOG performance status 2–3, and 65 (13%) patients with missing ECOG status, a population more in line with the European Medicines Agency (EMA) licence in this indication, which does not exclude based on performance status, than the CheckMate 141 trial. The clinical expert during the appraisal meeting confirmed that treatment with docetaxel is not considered to confer a survival benefit, and is reserved for symptomatic treatment of patients where the benefits may out-weigh the risks of toxicity. This is in alignment with the clinical feedback noted in the Company response to Technical Engagement that the majority of patients in UK clinical practice in this line of therapy would not receive docetaxel, and instead would receive no active treatment at all (i.e. palliative or best supportive care [BSC]); in many cases, this includes patients who are deemed to be clinically "fit enough" to receive docetaxel. As such, clinical expertise indicates that sufficient fitness does not necessarily mean that docetaxel would be received by these patients in the real-world setting. The Company are disappointed that this input provided during the appraisal from the clinical expert, who routinely treats patients with head and neck cancer in UK clinical practice, was dismissed by the Committee in favour of opinion of the Cancer Drugs Fund clinical lead without rationale. Therefore, while docetaxel represents the most relevant active comparator for nivolumab, the Company maintain that BSC remains a relevant comparator to this appraisal. Whilst the arguments outlined above for the relevance of the all-randomised population to inform the comparison of nivolumab versus docetaxel still stand, costs may be overestimated for the patient group as a whole if a large proportion of patients who are "fit enough" to receive docetaxel do not in fact receive it in clinical practice. As such, a scenario has been explored using the efficacy data from the all-randomised population where the acquisition and administration costs for docetaxel have been set to £0 (see Table 1); this results in only marginal increases in the ICER which remains	As for the patients with lower ECOG PS in the SACT dataset, the ERG would like to quote from the ERG critique of the company response to the technical report: *"The ToE also stated that patients not eligible for docetaxel would probably receive methotrexate. This would imply that the most appropriate CheckMate 141 data would be from those patients who would have been treated with methotrexate according to IC methotrexate subgroup)."* It is unclear to the ERG whether BSC would be an appropriate comparator or what constitutes BSC since it was not included in the ToE or in the original scope. Indeed, methotrexate was the comparator mentioned in the ToE for those not fit enough for a taxane.

<table>
<tr>
<td></td>
<td>below the willingness-to-pay threshold of £50,000, demonstrating the robustness of the ICER estimates and indicating that nivolumab is a cost-effective use of NHS resources.

Table 1: Cost-effectiveness results for the scenario analysis in which docetaxel acquisition and administration costs are set to zero in the all-randomised population using the full model (Model 1) utility
<table>
<tr><th>Assumption</th><th>ICER versus docetaxel (£/QALY gained)</th></tr>
<tr><td>Revised Company base case</td><td>43,207</td></tr>
<tr><td>No docetaxel acquisition and administration costs</td><td>44,597</td></tr>
</table>
Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9. Full details of the revised Company base case are presented in Appendix 1.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.</td>
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<tr>
<td>4</td>
<td>Section 3.4 (page 8): The ACD states: “The Cancer Drugs Fund Clinical Lead referred to an amendment update of the clinical protocol for CheckMate 141, which meant that people in the investigator-choice arm could have had nivolumab in the extension phase of the trial. The company did not provide data on how many people switched from investigator choice to nivolumab. It is therefore unclear how a treatment switch would have affected overall survival, which could potentially bias the results against nivolumab.”

The Company welcomes the acknowledgement by the Committee that the use of subsequent treatments or crossover in the IC arm could bias the results against nivolumab, and that use of these data without adjustment could represent a conservative approach.

As presented in Table 2, only [redacted] patients crossed over from the IC arm to nivolumab treatment as of the latest data cut of the CheckMate 141 trial (15th October 2019). However, all of these patients had received docetaxel, which may result in greater uncertainty in the survival estimates for the intended for docetaxel subgroup relative to the all-randomised population. In addition, several patients in both the all-randomised population and intended for docetaxel subgroup went on to receive subsequent immunotherapy, with a higher proportion of patients in the docetaxel arm of the intended for docetaxel subgroup receiving subsequent nivolumab ([redacted]% versus [redacted]%) and pembrolizumab ([redacted]% versus [redacted]%) compared with the IC arm as a whole. The Company note that</td>
<td>Given that only [redacted] patients crossed over from the comparator to the intervention arm, it is unlikely that any bias because of this would be substantial. It is difficult to predict what the combined effect of any subsequent therapy might have been. It is also uncertain as to the extent to which such therapy might be applicable to UK clinical practice. However, it is also the case that the percentage who received any subsequent therapy appears to be similar between arms in the docetaxel subgroup.</td>
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receipt of subsequent immunotherapy is not standard clinical practice in the UK, and this may also confound the results.

Table 2: Subsequent therapies received by patients in the nivolumab and Investigator's Choice arms of the all-randomised and intended for docetaxel populations

	All-randomised		Intended for docetaxel	
	Nivolumab (N=240)	IC (N=121)	Nivolumab (N=[redacted])	Docetaxel (N=[redacted])
Cross-over to nivolumab, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Any subsequent systemic therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Folic acid analogues	[redacted]	[redacted]	[redacted]	[redacted]
Other monoclonal antibodies [a]	[redacted]	[redacted]	[redacted]	[redacted]
Other immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy [b]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Taxanes	[redacted]	[redacted]	[redacted]	[redacted]

[a] Includes any monoclonal antibody except for nivolumab. [b] Includes both approved and experimental drugs.
Abbreviations: IC: Investigator's Choice.

5	**Section 3.5 (page 9):** The Committee conclude that there is evidence of nivolumab's benefit for tumours with a PD-L1 score of 1% or higher, but at a lower PD-L1 score the benefit is not clear. In Section 3.24 (page 21) of the published guidance from the original appraisal, the Committee concluded that the cost-effectiveness results for the PD-L1 subgroups are not suitable for decision making, citing them to be "*subject to uncertainty because of the small patient numbers and because*	The ERG would like to quote the ToE: *"The committee concluded that there is evidence of nivolumab's benefit in those with a PD-L1 expression of 1% or more, but for those with a PD-L1 expression of less than 1% the benefit is much less convincing…The*

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	CheckMate-141 was not powered to show a difference between the PD-L1 subgroups." Therefore, the Company are disappointed that the Committee have altered their conclusion on this topic, despite there being no change in the data available to inform it. Given this change in Committee conclusion, the Company would like to emphasise that CheckMate 141 was not powered to detect a difference between treatment arms in these subgroups, and that the patient numbers in these subgroups are small: [redacted] patients in the IC arm had confirmed PD-L1 <1%, of whom only [redacted] received docetaxel. As per the study protocol, these subgroups excluded patients in whom PD-L1 status could not be quantified; these patients represent 24% of the all-randomised population. Therefore, as well as the high degree of uncertainty introduced by small patient numbers in these groups, the exclusion of a substantial proportion of the study population from decision making could lead to patients within the NHS not having an effective treatment option available despite evidence in the all-randomised population indicating that they would benefit from nivolumab treatment. Furthermore, the use of these subgroups would provide insufficient evidence to address the decision problem of this appraisal as outlined in the final scope, which was to determine the clinical and cost-effectiveness of nivolumab within its anticipated marketing authorisation for treating recurrent or metastatic (R/M) squamous-cell carcinoma of the head and neck (SCCHN) after platinum-based therapy.[5] Furthermore, from the available data, the overlap between the 95% CI of HRs for nivolumab versus IC in the PD-L1 subgroups and the all-randomised population suggests that there is no statistically significant difference between the populations in terms of the treatment effect for OS (see Figure 4 in the original submission). Despite the 95% CIs overlapping 1 due to the small sample size, the point estimate of the HR indicates a treatment benefit with nivolumab versus IC (HR: 0.74) for the PD-L1 <1% subgroup. The Company welcome the Committee's acknowledgement of the feedback from the clinical expert that suggested PD-L1 score may not be a good predictor of treatment outcomes. As outlined in Comment 1, a significant unmet need irrespective of PD-L1 status remains in patients who would be eligible to receive nivolumab. Given the unmet need and the uncertainty associated with the results from the subgroup analyses based on PD-L1 expression, the all-randomised population should be considered as the patient population within the CDF review.	*committee are expecting the updated overall survival evidence from CheckMate-141 to include analysis by PD-L1 expression."* The ERG would also like to quote the ERG critique of the company response to the technical report: *"The ERG agrees that the PD-L1 status results need to be interpreted with caution. However, based on this evidence it does appear that PL-L1 status does affect the effectiveness of nivolumab and more so in the docetaxel subgroup, as shown by a larger difference in HRs between PD-L1 <1% and ≥1%."*

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6	**Section 3.7 (page 11):** The ACD states: "*the extrapolation of overall survival for the [intended for] docetaxel subgroup was uncertain because the assumptions had not been validated and reported with sufficient transparency*" and **Section 3.8 (page 11)** states: "*The most plausible extrapolation method for time to treatment discontinuation for the [intended for] docetaxel subgroup is unknown*". As outlined in Comment 2, the all-randomised population from the CheckMate 141 trial is the most appropriate data source for this appraisal, as it is adequately powered to detect differences between treatment arms and is most reflective of patients in this indication. However, for transparency, a detailed description of the survival analyses explored for the intended for docetaxel subgroup have been presented in Appendix 3 of this response document. Cost-effectiveness results for a variety of plausible extrapolation methods for OS and time to treatment discontinuation (TTD) have been presented in Appendix 2, as requested by the Committee. **Section 3.15 (page 16)**: The ACD notes that *"the committee agreed that the PD-L1 subgroups are of interest within the docetaxel population."* As outlined in Comment 2, the all-randomised population from the CheckMate 141 trial is the most appropriate data source for this appraisal. Additionally, the Committee fail to acknowledge that robust subgroup analyses by PD-L1 expression status within the intended for docetaxel subgroup are not feasible, given the small patient numbers within these groups. As presented in the Company response to Technical Engagement, in the intended for docetaxel subgroup, [redacted] patients had PD-L1 <1% ([redacted] received nivolumab and [redacted] received docetaxel) and [redacted] had PD-L1 ≥1% ([redacted] received nivolumab and [redacted] received docetaxel). Given the high degree of uncertainty introduced by the extremely small numbers of patients in each treatment arm within these subgroups, as well as the risk of selection bias due to broken randomisation, cost effectiveness results suitable for decision-making cannot be generated from these data. In particular, the Company note that, as outlined in Comment 5, the Committee originally identified the small patient numbers and lack of suitable statistical powering in the PD-L1 subgroups to render cost-effectiveness analyses in these subgroups to be unsuitable for decision making. It follows that the analysis of subgroups within these subgroups would be subject to even more uncertainty and are thus similarly inappropriate for decision making.	Please see previous response regarding subgroups based on PL-L1 status. The analyses provided in Appendix 3, based on the intended for docetaxel subgroup, are informative as this is according to the ACD the most appropriate data source (as also argued in the ERG report and in the ERG response above). However, none of the analyses provided by the company did incorporate all committee preferred assumptions simultaneously. According to the ACD, the committee preferred analyses would: • include data from the docetaxel subgroup only • include treatment-dependent and treatment-independent utility values • assume no treatment benefit for nivolumab 5 years after start of treatment • exclude the estimated utility decrements related to time before death • exclude the stopping rule. These assumptions have therefore been incorporated in the new ERG analyses (see separate document for results). Notably, the (intended for) docetaxel subgroup data is

		only used to estimate OS in the economic model, not for estimating PFS nor TTD. If, similarly as for OS, the relative benefit for PFS is reduced in this subgroup and/or the TTD is increased for instance as a result of the increased OS in this subgroup, then the current ERG ICERs are most likely underestimations.
7	**Section 3.10 (page 13):** The ACD summarises the Committee's discussion surrounding the duration of treatment benefit of nivolumab. In **Section 3.15 (page 15–16)** the Committee conclude that their preferred approach to modelling includes an assumption of no treatment benefit for nivolumab 5 years after start of treatment and exclusion of a stopping rule. The Company are disappointed that important evidence was omitted from this discussion, which has led to a misunderstanding surrounding the treatment benefit of nivolumab when no stopping rule is applied. As per the Company response to Technical Engagement, inspection of the log cumulative hazards plot for OS (Figure 13 of the original Company submission) clearly shows that towards the end of the observed follow-up period for CheckMate 141 there was a difference between treatment arms in the change in hazards over time, with a reduction in the hazard over time in the nivolumab arm and a relatively constant hazard in the IC arm. It is therefore not appropriate to assume that the hazard in the nivolumab arm becomes equal to the IC arm (i.e. there is no treatment benefit for nivolumab in the long term). This is consistent with the TA490 Committee's preference for the use of piecewise models to extrapolate OS, which are recommended in NICE Technical Support Document (TSD) 14 for modelling datasets in which variable hazards are observed over time. Given the maturity of the data from the CheckMate 141 trial (minimum follow-up of 48.2 months), and the fact that piecewise models were used to extrapolate OS, applying an additional treatment waning assumption in scenarios where no stopping rule is employed is counterintuitive. Accordingly, on Section 3.9 (page 12) of the ACD, it is noted that *"a clinical expert explained that people who are alive 5 years after treatment started are considered 'cured' from the disease."* Applying a treatment waning assumption from 5 years in the absence of a stopping rule is therefore	The ERG believes this response does not provide any new information or arguments. Hence, the ERG preferences regarding treatment waning (after 5 years) are still valid. The stopping rule should not be regarded as an argument against the 5-year treatment waning assumption. This is particularly the case given that the impact of the stopping rule on relative treatment effectiveness/ treatment effect waning is unknown based on data from the CheckMate 141 trial. The quote "a clinical expert explained that people who are alive 5 years after treatment started are considered 'cured' from the disease" might not be a relevant argument to exclude treatment waning after 5 years. This is because patients might be considered 'cured' for both treatments (if 'treatment' in this quote is referring to both nivolumab and docetaxel). Therefore, this quote might support assuming identical mortality rates

	not consistent with clinical reality, given patients alive at 5 years could be assumed to have a similar mortality risk to that of the general population. An updated plot of smoothed hazards over time (in months) is presented in Figure 3 (nivolumab and IC; all-randomised population), where a more appropriate scale has been applied. The plot shows a steeper reduction in hazards being observed in the IC arm compared to the nivolumab arm, and the curves have not yet converged. For the reasons outlined above, it is therefore not appropriate to apply a treatment waning assumption when no stopping rule is employed. **Figure 3: Smoothed hazards plot for nivolumab and IC overall survival (all-randomised population)**  **Abbreviations:** IC: investigator's choice.	post-5 years after treatment start. Of course, the number of patients alive at this point who might be assumed to have general population mortality might be higher in the nivolumab arm, but this does not imply that the mortality rate for each of those patients is any lower for those treated with nivolumab and thus treatment waning (equal mortality rate) would still be appropriate.

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8	**Section 3.10 (page 13):** The ACD notes that *"the committee considered that implementing a 2-year stopping rule for nivolumab could affect the relative treatment effect and cause the hazard rates to converge more quickly."* The Company would like to note that, as discussed further in Comment 7 and illustrated in Figure 3, convergence of the overall survival hazard rates for nivolumab IC has been misunderstood by the Committee. A difference between treatment arms in the change in hazards over time was observed towards the end of the follow-up period for CheckMate 141, indicating that hazard rates were not converging. As per the Company response to Technical Engagement, there is accumulating evidence to suggest that treatment with PD-L1 inhibitors, including nivolumab, may facilitate longer term benefit even following treatment discontinuation. In the CheckMate 141 trial, [redacted] of the 13 patients in the nivolumab arm who were alive and in follow-up at the time of the latest data cut [redacted] In addition, the Company note that implementation of a stopping rule is in line with the recommendation for pembrolizumab in the same indication (where a two year stopping rule was accepted as appropriate by the Committee) and with recommendations for nivolumab in other indications.[2, 6, 7] Given that clinical expert opinion suggests that patients who are in remission following treatment with nivolumab for five years may be considered functionally cured (ACD, Section 3.9), the Company present a revised base case in which a five-year stopping rule is implemented without a treatment waning assumption (full details of the revised base case are presented in Appendix 1). As discussed in Comment 7, applying a treatment waning assumption from 5 years in the absence of a stopping rule is not consistent with clinical reality, and is not supported by the data from the CheckMate 141 trial. Since patients in remission following treatment with nivolumab at the five year timepoints could be considered functionally cured, these arguments also apply when a 5 year stopping rule is implemented. As shown in Figure 4, in the revised Company base case the mortality rate associated with nivolumab is consistently higher than the mortality rate of the general population. As such, the survival for patients who are alive beyond the 5-year time point (and are considered functionally cured) may be underestimated in the base case, and thus the Company maintain that these base case assumptions are conservative.	The 5-year stopping rule proposed by the company is inconsistent with clinical evidence as well as the committee preference based on the ACD (stating to exclude the stopping rule). As highlighted in the previous response, statements such as "applying a treatment waning assumption from 5 years in the absence of a stopping rule is not consistent with clinical reality" are not supported by data from the CheckMate 141 trial and are thus potentially flawed. Moreover, as mentioned above the analyses provided by the company do not simultaneously include all committee preferred assumptions.

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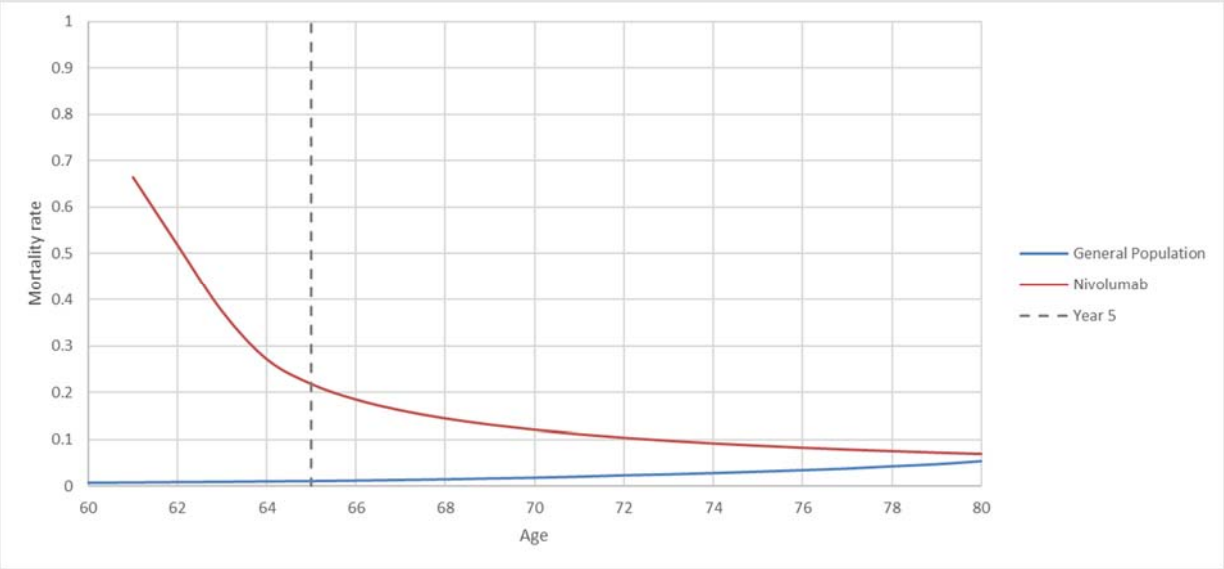
Figure 4: Mortality rate for the general population and nivolumab treatment arm of the CheckMate 141 trial over the model horizon in the revised Company base case



Full details of the revised Company base case are presented in Appendix 1.

The cost-effectiveness results of the revised company base case including the 5-year stopping rule and no treatment waning are presented in Table 3, including scenario analyses with the PD-L1 subgroups and when no stopping rule has been applied. Despite the fact that long-term survival for patients on nivolumab could be underestimated in the model, these results show that nivolumab is cost effective upon implementation of a five-year stopping rule, demonstrating it to be cost-effective use of NHS resources. Even when no stopping rule is applied, nivolumab remains cost-effective. For reference, the cost-effectiveness results for a variety of scenario combinations of stopping rules, treatment waning assumptions and utility assumptions in these populations are presented in Table 7, the majority of which produce ICERs of less than £50,000/QALY.

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Table 3: Cost-effectiveness results for the revised Company base case and one scenario combination of a treatment stopping rule and treatment waning assumption
<table>
<tr><th>Assumptions</th><th>ICER versus docetaxel (£/QALY)</th></tr>
<tr><td colspan="2">All-randomised population</td></tr>
<tr><td>5-year stopping rule, no treatment waning
(Revised Company base case)</td><td>43,207</td></tr>
<tr><td>No stopping rule, no treatment waning</td><td>48,442</td></tr>
<tr><td colspan="2">PD-L1 ≥1%</td></tr>
<tr><td>5-year stopping rule, no treatment waning</td><td>41,753</td></tr>
<tr><td>No stopping rule, no treatment waning</td><td>46,121</td></tr>
<tr><td colspan="2">PD-L1 <1%</td></tr>
<tr><td>5-year stopping rule, no treatment waning</td><td>48,576</td></tr>
<tr><td>No stopping rule, no treatment waning</td><td>48,576</td></tr>
</table>
Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9. Full details of the revised Company base case are presented in Appendix 1.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.
</td>
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<td>Section 3.11 (page 14): The ACD notes that “because no new evidence was presented on quality of life, the committee concluded that the most appropriate approach was to use both treatment-dependent and treatment- independent values in the base-case analysis.”

As discussed in response to ERG clarification question B7, no new analysis of utility data was conducted for the latest data cut of the Checkmate 141 trial, given that very few patients in either arm had remained in the trial and completed additional EQ-5D assessments. The Company acknowledge that uncertainty therefore remains in the most appropriate utility values for the model and that these values probably lie between the treatment-dependent and the treatment-independent estimates.</td>
<td>The ERG believes that the utilities provided in Table 4 of the company’s response might be a plausible alternative for the treatment dependent utility scenario (based on utility Model 1). However, the question remains how long the off-treatment utility gains for nivolumab should be extrapolated. Hence the ERG believes that the treatment independent utility scenario is still informative. For this purpose, utility Model 2 (which had the best statistical fit) could have provided plausible</td>
</tr>
</table>

	As described in the response to Technical Engagement, clinical expert feedback suggested that patients who remain on nivolumab for more than a few months and respond well to treatment are more likely to experience a utility benefit post-progression. The overall response rate (ORR) in CheckMate 141 was greater for nivolumab compared to IC (13.3% versus 5.8%), with a higher proportion of patients in the nivolumab arm achieving a best overall response of either a complete or partial response, as compared to the IC arm.[8] Nivolumab also offers a more durable response compared to IC, with responses maintained beyond 40 weeks for some patients in the nivolumab arm.[8] Therefore, whilst it is recognised that some patients receiving nivolumab may discontinue treatment or progress quickly (and therefore may be expected to have similar utility post-progression to patients who receive IC), the true utility values for the cohort as a whole may lie closer to treatment-dependent than to treatment-independent values. In addition, the mixed model that included progression status and treatment arm (used to derive treatment-specific utility values) was associated with a better statistical fit than the model including progression status alone (treatment-independent utility values). The ERG highlighted in their comments on the Company Technical Engagement response that regression Model 1 and Model 2 (which include a covariate for being off treatment), are associated with even better statistical fit. This approach has previously been accepted by NICE in an oncology indication.[9] Model 2 was considered to lack face validity since it does not include a parameter for progression status. A visual representation of the full model (Model 1), which includes progression status, treatment arm and treatment status, is presented in Figure 5. The derived utilities are presented in Table 4. Whilst this model still predicts a difference in utility between the "PD off-treatment" states for patients receiving nivolumab and IC, this difference is reduced compared to the model used to derive treatment-specific utility values. As such, the Company have updated their preferred base case to include utility values derived from the full model (Model 1), but for all scenarios presented in this response, results in which treatment-dependent and treatment-independent utility values are presented in Appendix 2 for the Committee's consideration. Estimated utility decrements related to time before death have been excluded in line with the Committee's preferred assumptions.	alternative utility values. Unfortunately, utility Model 2 was disregarded by the company, as it was "considered to lack face validity since it does not include a parameter for progression status" and therefore not considered in a scenario.

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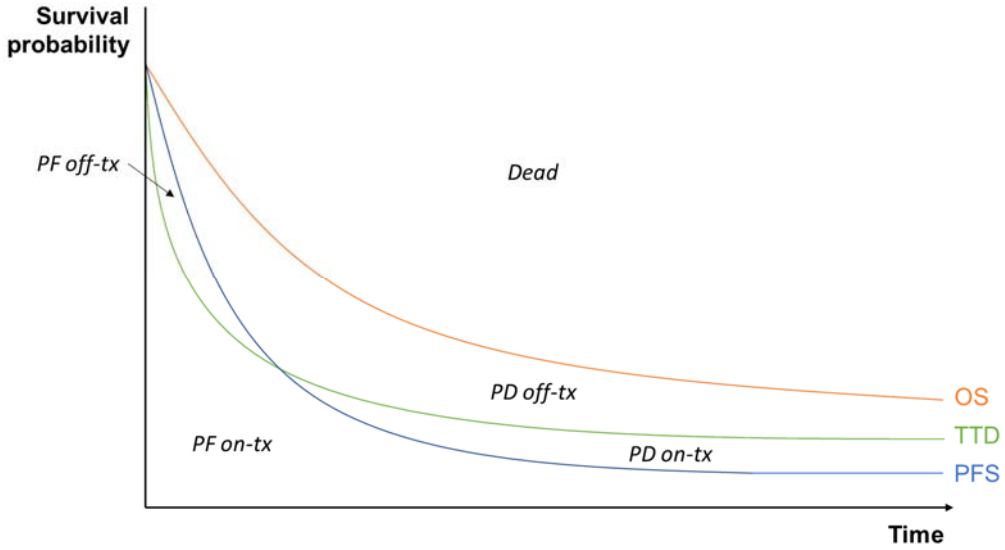
Figure 5: Visual representation of the full utility model



Abbreviations: OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; TTD: time to treatment discontinuation; tx: treatment.

Table 4: Utility values derived from Model 1 (full model)

	Nivolumab		IC	
	On-treatment	Off-treatment	On-treatment	Off-treatment
PF	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IC: investigator's choice; PD: progressed disease; PF: progression-free.

10	**Section 3.13 (page 14):** The ACD states that *"based on the evidence provided, the committee concluded that it is uncertain whether nivolumab would extend life by more than 3 months compared*	The use of undiscounted LYs to inform the end-of-life criteria seems appropriate to the

	with NHS standard care. Therefore, it is currently uncertain if nivolumab meets the end-of-life criteria when compared with docetaxel." **Section 3.14 (page 15):** The ACD further notes that "*The model estimates for the mean overall-survival benefit are 12 months for the PD-L1 1% and above subgroup, and 6.3 months for the PD-L1 less than 1% subgroup. Because of the uncertainty in the clinical evidence for the PD-L1 less than 1% subgroup, the committee concluded that it is uncertain whether the life-extending criterion was met in that subgroup*." As discussed further in Comment 2, the Company consider the all-randomised population to be the most relevant for this appraisal. In this population, the data confirm that nivolumab meets the end of life criteria as compared with IC. This conclusion was not identified as an area of uncertainty in the original appraisal process (TA490) where it was accepted by the Committee, and remains valid in the revised Company base case (see Appendix 1) where the estimated survival benefit for nivolumab as compared with IC is 5.4 months.[4] Therefore, the Company are disappointed that the Committee have changed their conclusion despite no change in the source of data informing the end of life criteria decision. A detailed description of the survival analyses explored for the intended for docetaxel subgroup has been provided in Appendix 3 of this response document, which should resolve any uncertainty in the extrapolations of OS and TTD. The ACD reports that the mean OS benefit for nivolumab was estimated to be [redacted] months in the intended for docetaxel subgroup. It appears this result has been calculated based on the discounted life years gained (LYG); survival benefit should in fact be based on undiscounted LYG. Mean survival for nivolumab and the comparator in the docetaxel and PD-L1 <1% subgroups using a range of extrapolation methods for OS are presented in Table 9, alongside the estimated survival benefit for nivolumab. In both subgroups, nivolumab is associated with a survival benefit of considerably more than 3 months versus IC for all OS extrapolations explored. Whilst uncertainty remains in the underlying data for these subgroups given they are derived from small sample sizes, the durability in the survival benefit across a range of extrapolation methods confirm that nivolumab meets the end-of-life criteria within these subgroups.	ERG. However, as highlighted above, the cost-effectiveness analyses submitted by the company do not simultaneously include all committee preferred assumptions.

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Table 5: Estimated survival benefit for nivolumab for a variety of extrapolation methods

Extrapolation method for OS [a]	Mean survival (months)		Survival benefit for nivolumab (months)
	Nivolumab	IC/docetaxel	
Intended for docetaxel subgroup			
Piecewise lognormal 96-week cut-off	[redacted]	[redacted]	[redacted]
Piecewise lognormal 48-week cut-off	[redacted]	[redacted]	[redacted]
Fully parametric lognormal	[redacted]	[redacted]	[redacted]
Fully parametric loglogistic	[redacted]	[redacted]	[redacted]
PD-L1 <1% subgroup			
Piecewise lognormal 48-week cut-off	[redacted]	[redacted]	[redacted]
Fully parametric lognormal	[redacted]	[redacted]	[redacted]
Fully parametric loglogistic	[redacted]	[redacted]	[redacted]

[a] In the docetaxel subgroup, the exploratory extrapolation method for OS was applied to both the nivolumab and IC treatment arms. In the PD-L1 <1% subgroup, the exploratory extrapolation method for OS was applied to the nivolumab treatment arm only, given that [redacted]

Insert extra rows as needed

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Appendix 1 – Revised Company base case results

The inputs implemented in the revised Company base case are as follows:

- Population: all-randomised
- Stopping rule: 5 years
- Treatment waning: None
- OS extrapolation: 96-week lognormal for nivolumab arm; 96-week lognormal for IC arm
- PFS extrapolation: generalised gamma for nivolumab arm; generalised gamma for IC arm
- TTD extrapolation: 2-spline normal for nivolumab arm; [redacted] for IC arm
- Utility values: full model (Model 1)

The cost-effectiveness results of the revised Company base case are presented in Table 6.

Table 6: Revised Company base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Docetaxel	10,561	0.67	0.35	[redacted]	0.65	[redacted]	£43,207

Note that time-to-death utility decrements have not been applied.
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

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Appendix 2 – Additional cost-effectiveness results in the all-randomised population and PD-L1 subgroups

Table 7: Cost-effectiveness results for various combinations of a treatment stopping rule, treatment waning assumption and utility assumption

Assumptions	ICER versus docetaxel (£/QALY)		
	Full model (Model 1) *Base case assumption*	Treatment-specific utility	Treatment-independent utility
All-randomised (base case) population			
2-year stopping rule No treatment waning *(Company base case at TE)*	36,802	35,357	41,557
2-year stopping rule 3-year treatment waning	50,336	49,168	60,529
2-year stopping rule 5-year treatment waning	43,601	42,222	50,748
5-year stopping rule 5-year treatment waning	51,305	49,682	59,714
5-year stopping rule **No treatment waning** ***(Revised Company base case)***	**43,207**	**41,511**	**48,789**
No stopping rule No treatment waning	48,442	46,540	54,700
PD-L1 ≥1%			

2-year stopping rule No treatment waning	36,039	34,718	38,980
2-year stopping rule 3-year treatment waning	48,291	47,325	54,386
2-year stopping rule 5-year treatment waning	42,179	40,958	46,493
5-year stopping rule 5-year treatment waning	48,965	47,548	53,972
5-year stopping rule No treatment waning	41,753	40,222	45,160
No stopping rule No treatment waning	46,121	44,430	49,885
PD-L1 <1%			
2-year stopping rule No treatment waning	44,771	43,181	54,041
2-year stopping rule 3-year treatment waning	56,851	54,990	72,804
2-year stopping rule 5-year treatment waning	50,048	48,319	61,947
5-year stopping rule 5-year treatment waning	54,339	52,462	67,258
5-year stopping rule No treatment waning	48,576	46,851	58,634
No stopping rule	48,576	46,851	58,634

No treatment waning			

Note that time-to-death utility decrements have not been applied in these scenarios. The utility values derived from the full model (Model 1) are presented in Comment 9.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; TE: Technical Engagement.

Table 8: Cost-effectiveness results for the all-randomised (base case) population using alternative OS and TTD extrapolations

Scenario	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on ICER (£)
Revised base case	**OS:** Piecewise lognormal 96-week cut-off for both nivolumab and docetaxel **TTD:** 2-spline normal for nivolumab, [redacted]	43,207	-
Alternative OS assumption	Piecewise lognormal 48-week cut-off for both nivolumab and IC	46,286	+3,079
Alternative OS assumption	Fully parametric lognormal for both nivolumab and IC	47,314	+4,107
Alternative OS assumption	Fully parametric loglogistic for both nivolumab and IC	45,068	+1,861
Alternative TTD assumption	Generalised gamma for both nivolumab and IC	42,436	−771

Abbreviations: K-M: Kaplan-Meier; IC: Investigator's choice; ICER: incremental cost effectiveness ratio; OS: overall survival; TTD: time to treatment discontinuation.

Appendix 3 – Survival assumptions and cost-effectiveness results for the intended for docetaxel subgroup

Overall survival

As per the Committee's preferred approach in TA490 and in alignment with the additional analysis presented by the Company at Technical Engagement, the piecewise method was used to extrapolate OS for the intended for docetaxel subgroup. The distributions that were explored were the exponential distribution, as recommended in Bagust and Beale (2014), and also the lognormal distribution, which represented the Committee's preferred extrapolation in TA490.[10] To inform the

choice of timepoint to extrapolate from, the log-cumulative hazards plot was inspected (see Figure 6). As for the all-randomised population, there is a noticeable change in hazard from Week 20 in both treatment arms. For IC (docetaxel), the hazard appears to be relatively constant over time from Week 20 onwards, whereas for nivolumab there is a trend towards a reduction in the hazard over time, which would favour the use of the lognormal distribution.

Visual inspection of these piecewise extrapolations compared to the observed trial data showed that the exponential distributions produced a poorer fit than the lognormal distributions (see Figure 7). When looking only at the lognormal distribution, the visual fit was fairly similar across the timepoints explored, with both providing a reasonable fit to the observed trial data. Only the piecewise models using the lognormal distribution were therefore considered for the intended for docetaxel subgroup, with preference given to the Week 96 timepoint in order to maximise the use of observed trial data.

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Figure 6: Log cumulative hazard plot for overall survival in the intended for docetaxel subgroup

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Figure 7: Long-term OS extrapolation using piecewise models for nivolumab and IC (intended for docetaxel subgroup)

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

In addition to the piecewise models, fully parametric extrapolations of the observed data were also explored. AIC and BIC values for each fully parametric survival model are presented in Table 9, and the long-term extrapolations of OS using each model are presented in Figure 8 and Figure 9, for nivolumab and docetaxel, respectively. As per the all-randomised population, the fully parametric lognormal curve was associated with the best statistical fit to both the nivolumab and

docetaxel arms, and provided a reasonable visual fit to the observed data from the intended for docetaxel subgroup. The loglogistic curve, which is also associated with decreasing hazards over time, also provided a reasonable fit to the observed data and was one of the better fitting non-spline curves in terms of AIC and BIC. Long-term extrapolations using the fully parametric lognormal and loglogistic models are presented in Figure 10, alongside the lognormal piecewise models.

Based on the above, the fully parametric models are still considered to provide plausible extrapolations of OS with nivolumab and docetaxel and therefore have been explored in scenario analyses, alongside the 96-week piecewise model that represented the base case approach for the all-randomised population.

Table 9: Summary of goodness-of-fit data for overall survival – intended for docetaxel subgroup

Distribution	Nivolumab		Docetaxel	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each arm is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

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Figure 8: Long-term OS extrapolation of parametric and piecewise models for nivolumab (intended for docetaxel subgroup)

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

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Figure 9: Long-term OS extrapolation of parametric and piecewise models for docetaxel (intended for docetaxel subgroup)

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

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Figure 10: Long-term OS extrapolation using fully parametric lognormal and loglogistic models, and piecewise models for nivolumab and docetaxel (intended for docetaxel subgroup)

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

Progression-free survival

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A variety of parametric and spline models were explored to extrapolate PFS for the intended for docetaxel subgroup. AIC and BIC values for each survival model are presented in Table 10, and the long-term extrapolations of PFS using each model are presented in Figure 11 and Figure 12 for nivolumab and docetaxel, respectively.

Of those explored, the spline models provided a better statistical fit for nivolumab than the standard parametric models, but the best-fitting curves often produced logical inconsistencies when compared to the preferred extrapolation for OS (with or without the treatment waning effect applied), whereby PFS was higher than OS. Excluding the spline models, the lognormal and loglogistic models provided the best statistical fit for docetaxel but were associated with a poor statistical and visual fit to the observed data for nivolumab in the long term. The generalised gamma model provided the best statistical fit for nivolumab and good visual fit to both arms was therefore explored for alignment with the all-randomised population (Figure 13).

Table 10: Summary of goodness-of-fit data for progression-free survival – intended for docetaxel subgroup

Distribution	Nivolumab		Docetaxel	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each arm is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

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Figure 11: Long-term PFS extrapolation of parametric models for nivolumab (intended for docetaxel subgroup)

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

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Figure 12: Long-term PFS extrapolation of parametric models for docetaxel (intended for docetaxel subgroup)

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

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Figure 13: Long-term PFS extrapolation of most plausible models for nivolumab and docetaxel (intended for docetaxel subgroup)

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

Time to treatment discontinuation

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As for PFS, a variety of parametric and spline models were explored to extrapolate TTD for the intended for docetaxel subgroup. AIC and BIC values for each survival model are presented in Table 11, and the long-term extrapolations of TTD using each model are presented in Figure 14 and Figure 15 for nivolumab and docetaxel, respectively.

[redacted]. For nivolumab, as per the all-randomised population, the spline models were associated with the best statistical fit. Of these, the 2 spline normal model provided the best statistical fit and a reasonable visual fit to the observed data. Additionally, compared with mean PFS, mean TTD predicted by the model [redacted]. The 2 spline normal model was therefore considered to be most plausible extrapolation of TTD. However, in alignment with the ERG preferences for the all-randomised population, the generalised gamma model was also explored for extrapolation of the nivolumab and docetaxel arms (Figure 16).

Table 11: Summary of goodness-of-fit data for time to treatment discontinuation – intended for docetaxel subgroup

Distribution	Nivolumab		Docetaxel	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Odds	[redacted]	[redacted]	[redacted]	[redacted]
1-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]
2-Spline Normal	[redacted]	[redacted]	[redacted]	[redacted]

A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each arm is **bolded**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

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Figure 14: Long-term TTD extrapolation of parametric models for nivolumab (intended for docetaxel subgroup)

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

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Figure 15: Long-term TTD extrapolation of parametric models for docetaxel (intended for docetaxel subgroup)

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

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Figure 16: Long-term TTD extrapolation of most plausible models for nivolumab and IC (intended for docetaxel subgroup)

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

Cost-effectiveness data in the intended for docetaxel subgroup

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Table 12: Cost-effectiveness results for the intended for docetaxel subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Intended for docetaxel subgroup [a]							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Docetaxel	11,213	0.85	0.44	[redacted]	0.56	[redacted]	51,342
Scenario: intended for docetaxel subgroup with treatment-specific utility							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Docetaxel	11,213	0.85	0.46	[redacted]	0.56	[redacted]	51,897
Scenario: intended for docetaxel subgroup with treatment-independent utility							
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Docetaxel	11,213	0.85	0.52	[redacted]	0.56	[redacted]	62,381

Note that time-to-death utility decrements have not been applied in these scenarios.
[a] This subgroup analysis was run using assumptions matching those employed in the revised Company base case, including utilities derived from the full model (Model 1). See Appendix 1 for full details.
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

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Table 13: Cost-effectiveness results for the intended for docetaxel subgroup for alternative OS and TTD extrapolations

Scenario in the intended for docetaxel subgroup	Scenario detail	ICER vs docetaxel (£/QALY gained)	Impact on ICER (£)
Revised base case assumptions [a]	**OS:** Piecewise lognormal 96-week cut-off for both nivolumab and docetaxel **TTD:** 2-spline normal for nivolumab, [redacted]	51,342	-
Alternative OS assumption	Piecewise lognormal 48-week cut-off for both nivolumab and docetaxel	54,563	+3,221
Alternative OS assumption	Fully parametric lognormal for both nivolumab and docetaxel	54,874	+3,532
Alternative OS assumption	Fully parametric loglogistic for both nivolumab and docetaxel	50,800	−542
Alternative TTD assumption	Generalised gamma for both nivolumab and docetaxel	49,514	−1,828
Revised base case assumptions using TS and TI	**OS:** Piecewise lognormal 96-week cut-off for both nivolumab and docetaxel **TTD:** 2-spline normal for nivolumab, [redacted]	TS: 51,897 TI: 62,381	-
Alternative OS assumption	Piecewise lognormal 48-week cut-off for both nivolumab and docetaxel	TS: 55,322 TI: 66,898	TS: +3,425 TI: +4,517
Alternative OS assumption	Fully parametric lognormal for both nivolumab and docetaxel	TS: 55,671 TI: 67,429	TS: +3,774 TI: +5,048
Alternative OS assumption	Fully parametric loglogistic for both nivolumab and docetaxel	TS: 51,215 TI: 61,880	TS: −682 TI: −501
Alternative TTD assumption	Generalised gamma for both nivolumab and docetaxel	TS: 51,815 TI: 62,283	TS: −82 TI: −98

Note that time-to-death utility decrements have not been applied in these scenarios.

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

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 28 January 2021 via NICE DOCS

[a] This subgroup analysis was run using assumptions matching those employed in the revised Company base case, including utilities derived from the full model (Model 1). See Appendix 1 for full details.
Abbreviations: FM: full model; ICER: incremental cost effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; TI: treatment-independent utility; TS: treatment-specific utility; TTD: time to treatment discontinuation.

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

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 28 January 2021 via NICE DOCS

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The company has provided an updated PAS for nivolumab of [redacted]. Using the model submitted by the company on February 1 ("ID1585 nivolumab BMS CEM revised base case after ACM 01022021CM [ACIC].xlsm") the ERG was able to reproduce the company's revised base-case results (with updated PAS). Specifically, this included those assumptions mentioned in Table 2 for the revised Company base case (5-year stopping rule, no treatment waning):

- Company base-case (treatment-specific utility values based on Model 1): £40,069 per QALY gained;
- Treatment-specific utility scenario (utility values based on Model 6): £38,496 per QALY gained and;
- Treatment-independent utility scenario (utility values based on Model 7): £45,245 per QALY gained

Table 1: ERG post ACD analyses (deterministic), nivolumab with updated PAS for nivolumab

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Nivolumab ICER (£/QALY gained)
ERG base-case 1 (as in original ERG report) Original company base-case (as in original CS) + OS treatment waning (5 year after treatment start) + generalised gamma model for estimating TTD + excluding the 2-year stopping rule					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.35	[redacted]	[redacted]	£49,559
ERG base-case 2 (as in original ERG report) Original company base-case (as in original CS) + OS treatment waning (5 year after treatment start) + generalised gamma model for estimating TTD + excluding the 2-year stopping rule + treatment independent utility					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£10,497	0.38	[redacted]	[redacted]	£55,684
Revised ERG base-case 1 ERG base-case 1 (as in original ERG report) + OS estimated based on data from the (intended for) docetaxel subgroup only					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,131	0.46	[redacted]	[redacted]	£64,691
Revised ERG base-case 2 ERG base-case 2 (as in original ERG report) + OS estimated based on data from the (intended for) docetaxel subgroup only					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,131	0.49	[redacted]	[redacted]	£74,799
Scenario: revised ERG base-case 1 plus excluding time before death utility decrements					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,131	0.46	[redacted]	[redacted]	£60,625
Scenario: revised ERG base-case 2 plus excluding time before death utility decrements					
Nivolumab	[redacted]	[redacted]			
Docetaxel	£11,131	0.52	[redacted]	[redacted]	£75,171
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; TTD = time to treatment discontinuation					

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

BMS response following Appraisal Committee Meeting 2 held on 17th June 2021

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

Bristol-Myers Squibb Pharmaceuticals Ltd

July 2021

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

Updated cost-effectiveness analysis

[redacted]

The tables below show the updated cost-effectiveness analysis based on the committee's preferences [redacted]

Table 1. Committee-preferred cost-effectiveness analysis [redacted]

	Arm	Total costs (£)	Total QALYs	Total life years	Inc. costs (£)	Inc. QALYs	Inc. life years	ICER (£/QALY)
Treatment-dependent utilities	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Doxetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-dependent utilities	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Doxetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER: incremental cost-effectiveness ratio; Inc.: incremental; QALY: quality-adjusted life year							

Table 2. Committee-preferred cost-effectiveness analysis [redacted]

	Arm	Total costs (£)	Total QALYs	Total life years	Inc. costs (£)	Inc. QALYs	Inc. life years	ICER (£/QALY)
Treatment-dependent utilities	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Doxetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-dependent utilities	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Doxetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER: incremental cost-effectiveness ratio; Inc.: incremental; QALY: quality-adjusted life year							