NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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. **Comments on the Appraisal Consultation Document from Merck Sharp & Dohme**
   a. Main response
   b. Appendix to response

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Joint response from the Royal College of Physicians

   There were no responses to the consultation from the invited experts or through the website consultation.

4. **Evidence Review Group critique of company comments on the ACD**

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

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer

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	Consultee	Merck Sharp & Dohme	A full comparison between treatment arms of baseline patient characteristics for the 2 subgroups (patients whose cancer started inside the oral cavity, and patients whose cancer started outside the oral cavity), of the KEYNOTE-048 study, are provided in Appendix 1 of the appendices document attached to this comments form. **Summary of imbalances in baseline characteristics between treatment arms** <u>Patients whose cancer originated in the oral cavity and with PD-L1 combined positive score (CPS) ≥1</u> *Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy* Table 1 of Appendix 1 of the appendices document attached to this comments form provides a summary of the baseline characteristics for the comparison of pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1. Given the small size of this sub-population (pembrolizumab monotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]), certain imbalances in baseline characteristics between treatment groups were observed. In cases where imbalances were noted, the magnitude of the imbalances were small, falling within the range of a 5% to 15% difference between treatment groups, with the exception of [redacted] ([redacted] difference across groups). Among continuous variables, the median time from latest platinum therapy was shorter for pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy; however, given the small subgroup of patients with prior platinum therapy (pembrolizumab monotherapy: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]) the influence of any imbalance in this factor on overall survival (OS) could be considered minimal. The following is a summary of the slight imbalances in baseline characteristics identified for the comparison of pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy: • Gender: [redacted] proportion of females in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Geographic region group: [redacted] proportion of patients from North America in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]), and [redacted] proportion from the rest of world (pembrolizumab monotherapy arm: [redacted];	Thank you for submitting the evidence on baseline patient characteristics for the 2 subgroups (patients whose cancer started inside the oral cavity, and patients whose cancer started outside the oral cavity). The committee noted that there were no obvious imbalances in patient baseline characteristics that would favour either the pembrolizumab or comparator arms of the trial. But it considered that characteristic imbalances should still be adjusted for when analysing clinical effectiveness in the 2 subgroups, to capture potential effects on the relative treatment effect and the general prognosis. The committee agreed that the analyses provided by the company did not fully satisfy what it had requested, meaning the clinical effectiveness outcomes were uncertain, but the extent and direction of this uncertainty was not known. Please see section 3.7 of the FAD for a summary of this discussion.

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			cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]). • Smoking status: [redacted] proportion of never smokers in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • PD-L1 tumour positive score (TPS) status ≥50%: [redacted] proportion of patients with strongly positive PD-L1 status (TPS≥50%) in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Disease status: [redacted] proportion of patients with metastatic disease status in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Time from latest platinum therapy: Median time from latest platinum therapy was [redacted] for the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]); however, given the small size of the subgroup of patients with prior platinum therapy (pembrolizumab monotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]) the influence of any imbalance in this factor on OS could be considered minimal. *Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy* Table 2 of Appendix 1 of the appendices document attached to this comments form provides a summary of the baseline characteristics for the comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy arm versus cetuximab in combination with platinum and 5-FU chemotherapy arm in patients with tumours that originated in the oral cavity and with PD-L1 CPS≥1. Given the small size of this sub-population (pembrolizumab in combination with platinum and 5-FU chemotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]), certain imbalances in baseline characteristics between treatment groups were observed. In all cases where imbalances were noted, the magnitude of the imbalances were small, falling within the range of a 5% to 15% difference between treatment groups. Among continuous variables, the median time from latest platinum therapy was shorter for the pembrolizumab in combination with platinum and 5-FU chemotherapy arm versus the cetuximab in combination with platinum and 5-FU chemotherapy arm; however, given the small size of this subgroup of patients with prior platinum therapy (pembrolizumab in combination with platinum and 5-FU chemotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]) the influence of any imbalance in this factor on OS could be considered minimal. The following is a summary of the slight imbalances in baseline characteristics identified for the comparison of the pembrolizumab in combination with platinum and 5-FU chemotherapy arm versus the cetuximab in combination with platinum and 5-FU chemotherapy arm:	

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			• Gender: [redacted] proportion of females in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Age: [redacted] proportion of patients with age ≥65 years in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Geographic region group: [redacted] proportion of patients from North America in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Smoking status: [redacted] proportion of current smokers in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • ECOG: [redacted] proportion of patients with ECOG 0 in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • PD-L1 TPS≥50%: [redacted] proportion of patients with strongly positive PD-L1 status (TPS≥50%) in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • PD-L1 CPS≥20: [redacted] proportion of patients with strongly positive PD-L1 status CPS≥20 in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Baseline tumour size (grouping by intention-to-treat [ITT] median): [redacted] proportion with tumour size ≥median in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Time from latest platinum therapy: Median time from latest platinum therapy was [redacted] in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]); however, given the small size of the subgroup of patients with prior platinum therapy (pembrolizumab in combination with platinum and 5-FU chemotherapy arm: [redacted]; the cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]) the influence of any imbalance in this factor on OS could be considered minimal. <u>Patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1</u>	

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			Table 3 and Table 4 of Appendix 1 of the appendices document attached to this comments form provide a summary of the baseline characteristics for the comparison of pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, and pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, respectively, in patients whose tumours originated outside of the oral cavity and with PD-L1 CPS≥1. Baseline characteristics were generally well balanced across treatment groups. In cases where imbalances were noted, the magnitude of the imbalances were small, falling within the range of a 5% to 10% difference between treatment groups. *Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy* The following is a summary of the slight imbalances in baseline characteristics identified for the comparison of the pembrolizumab monotherapy arm versus the cetuximab in combination with platinum and 5-FU chemotherapy arm: • Geographic region group: [redacted] proportion of patients from Europe in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]), and [redacted] proportion from rest of world (pembrolizumab monotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]). • Time from latest platinum therapy: median time from latest platinum therapy was [redacted] in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). *Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy* The following is a summary of the slight imbalances in baseline characteristics identified for the comparison of the pembrolizumab in combination with platinum and 5-FU chemotherapy arm versus the cetuximab in combination with platinum and 5-FU chemotherapy arm: • Gender: [redacted] proportion of females in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Disease status: [redacted] proportion of patients with metastatic disease status in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). Time from latest platinum therapy: median time from latest platinum therapy was [redacted] in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).	

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2	Consultee	Merck Sharp & Dohme	Overall survival data (Kaplan-Meier curves, hazard ratios) for the 2 subgroups (patients whose cancer started inside the oral cavity, and patients whose cancer started outside the oral cavity), of the KEYNOTE-048 study, are provided in Appendix 3 of the appendices document attached to this comments form. Subgroup analyses of overall survival to relevant prognostic factors To further understand the potential influence of any slight imbalances on OS, subgroup analyses of OS from the KEYNOTE-048 study according to each relevant prognostic factor were conducted separately within the population of patients with tumours that originated in the oral cavity and PD-L1 CPS≥1 (Figures 1 and Figure 2 in Appendix 2 of the appendices document attached to this comments form), and within the population of patients with tumours that originated outside of the oral cavity and PD-L1 CPS≥1 (Figures 3 and Figure 4 pf the appendices document attached to this comments form). As shown in the forest plots for both the comparison of pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, and pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, within each sub-population, analyses of OS according to each relevant prognostic factor were consistent with the primary findings, with all 95% confidence intervals in the subgroup analyses overlapping the 95% confidence interval of the hazard ratio of the primary analysis. Therefore, given that the relative treatment effects on OS did not appear to differ by the baseline characteristics that were found to be slightly imbalanced, there is no evidence to suggest that approaches to adjust for the slight imbalances in certain prognostic factors would materially impact the OS results. Methodological options considered for adjusting survival curves for potential imbalances in prognostic factors between treatment arms The committee has recommended that NICE requests an adjustment of the oral cavity and non-oral cavity OS Kaplan-Meier curves and hazard ratios for imbalances in baseline patient characteristics in the subgroups and further advised to not restrict it to just the covariates that are unbalanced, referencing NICE Decision Support Unit Technical Support Document 17. The reference document provides guidance on methods used with observational data, and while it does provide some guidance on adjustments for prognostic factors on outcomes (regression adjustment, multivariate regression, propensity score, or instrumental variables) within observational data, there is minimal discussion within this document related to case-control studies and no discussion related specifically to the adjustment of survival data within economic models. We have identified two key methods that one can use, within an economic model using survival curves, in order to address issues related to confounding bias: the average covariate method and corrected group prognostic method. 1. The first method, the average covariate method, provides covariate adjusted Kaplan-Meier curves. This method is ideally suited to predicting survival in a particular subgroup. However, importantly, it assumes the variables that are adjusted are continuous covariates. This adjusted curve is designed to represent a “hypothetical average individual.” 2. The second method, the corrected group prognostic method, is a “bottom- up group average	Thank you for submitting this evidence. The committee discussed the overall survival analyses by baseline characteristics for the 2 subgroups (patients whose cancer started inside the oral cavity, and patients whose cancer started outside the oral cavity). It agreed that the analyses provided by the company did not fully satisfy what it had requested, meaning the clinical effectiveness outcomes were uncertain, but the extent and direction of this uncertainty was not known. Please see section 3.7 of the FAD for a summary of this discussion.

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			approach" (https://doi.org/10.1093/oxfordjournals.aje.a008670, https://doi.org/10.1001/jama.286.12.1494, https://doi.org/10.1007/s10985-008-9098-9). One develops survival curves using the estimated coefficients from the Cox proportional hazards model and then calculates a weighted survival average curve combining the individually estimated curves. This method is ideally suited to predicting survival in a heterogenous group of individuals. It also assumes that the variables being adjusted are categorical covariates (or recoded continuous variables). This curve represents a grouped population average. Both adjustment methods have been previously presented to NICE as part of a technology appraisal for lenvatinib for untreated advanced hepatocellular carcinoma (NICE appraisal ID1089 resulting in NICE technology appraisal guidance TA551), with the limitations of both methods noted. The adjustments were conducted to address imbalances for key baseline characteristics. It is worth noting that in the case of the REFLECT trial that although two different adjustments were presented and acknowledging the imbalances, the committee acknowledged that the data within the trial itself was relevant to clinical practice (https://www.nice.org.uk/guidance/ta551/chapter/3-Committee-discussion): "The company highlighted that in REFLECT, more people in the lenvatinib group had alpha-fetoprotein levels of 200 ng/ml or above compared with the sorafenib group, and there were differences in the pre-existing liver conditions associated with hepatocellular carcinoma (hepatitis C, hepatitis B or alcohol) across the 2 groups. The company explained that these variables were not included as randomisation stratification factors. It considered that these imbalances in baseline characteristics may affect the treatment benefit seen with lenvatinib because they were potentially important prognostic factors. However, the clinical experts explained that a similar treatment benefit was likely regardless of pre-existing liver conditions." In the case of prognostic variable adjustment within specific subgroups of the KEYNOTE-048 study, at first pass it seems that between the two methods, the average covariate method would be most appropriate and perhaps the most straight forward method to more carefully examine the individual subgroups, especially given the committee's request to adjust multiple variables. However, upon careful review of potential variables of concern, within the subgroups, it appears that additional adjustment within this case-control trial could introduce greater uncertainty and perhaps bias within the model for reasons further specified in the following section. Consideration of confounding among prognostic variables in KEYNOTE-048 When considering specific variables for adjustment, it is important to first understand which of these variables are causally related to the disease. If the purported confounders are in fact causally related to the disease, then it is, of course, appropriate to use them as adjustment variables. If this step is carelessly done and unnecessary confounders are incorporated into the analysis two things could occur: 1. Extra variability would be introduced into the estimates of risk.	

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			2. Bias could be introduced by (unintentionally or intentionally) selecting confounders that most reduce the disease-exposure association. Upon examination of the forest plots of the subgroup analyses of overall survival to relevant prognostic factors described previously (Figures 1-4 of Appendix 2 of the appendices document attached to the comments form), all of the variables for both the oral cavity primary tumour and non-oral cavity primary tumour analyses had overlapping confidence intervals and no obvious patterns were seen between the prognostic factors when examining both the different treatment groups as well as the different subgroups. If some of the more extreme examples are examined, for example, [redacted] in the oral cavity primary tumour CPS≥1 group of the pembrolizumab in combination with platinum and 5-FU chemotherapy treatment arm, it visually has the largest difference among the prognostic factors (Figure 1), recognising that the confidence intervals do overlap and the total n for each arm is [redacted] and [redacted] for the pembrolizumab in combination with platinum and 5-FU chemotherapy treatment arm and the cetuximab in combination with platinum and 5-FU chemotherapy arm, respectively. However, when one then looks at the same subgroup (oral cavity primary tumour CPS≥1) for pembrolizumab monotherapy arm compared to the cetuximab in combination with platinum and 5-FU chemotherapy arm, this imbalance is absent (Figure 2). This is also not an obvious variable of interested among the non-oral cavity primary tumour patients (Figures 3-4). This indicates that [redacted] is likely not an appropriate prognostic factor to adjust for and if adjusted, could potentially insert bias and variability. Upon careful review, no prognostic factors were identified that would be of obvious value to adjust for, especially given that this is a case-control study. For these reasons, OS adjustments for imbalances in baseline characteristics in the oral cavity primary tumour and non-oral cavity primary tumour subgroups of the KEYNOTE-048 trial have not been applied.	
3	Consultee	Merck Sharp & Dohme	The NICE DSU Technical Support Document 14 was used as the basis for extrapolation curve selection. The methods employed were: • AIC/BIC test (statistical test) • External data validation • Clinical validity **<u>Oral Cavity Subgroup</u>** The statistical test showed the Log-normal to have the second-best ranking in the pembrolizumab monotherapy and combination therapy regimens as can be seen in Table 25 in Appendix 4. With the five-year treatment waning effect applied, this results in a 5- and 10-year overall survival of 11.3% and 4.5% respectively for pembrolizumab monotherapy. With the five-year treatment waning effect applied this results in a 5- and 10-year overall survival of 10.8% and 4.3% respectively for pembrolizumab combination therapy as can be seen in Table 31. Clinical expert feedback to MSD on overall survival was in the range of 14 – 19% at 5 years; hence, when considering external validation, this is a highly conservative survival extrapolation for pembrolizumab monotherapy and combination therapy. Graphs representing the overall survival in both regimens can be found below. Making use of 5-year follow-up data from other pembrolizumab clinical studies, as referenced in the long-term	Thank you for submitting this data. The committee discussed different extrapolation methods for the 2 subgroups (patients whose cancer started inside the oral cavity, and patients whose cancer started outside the oral cavity). It concluded that the log-normal extrapolations gave clinically implausible results, and that the Weibull distributions were more appropriate for decision making. Please see section 3.11 of the FAD for a summary of the committee's discussion. The committee noted that

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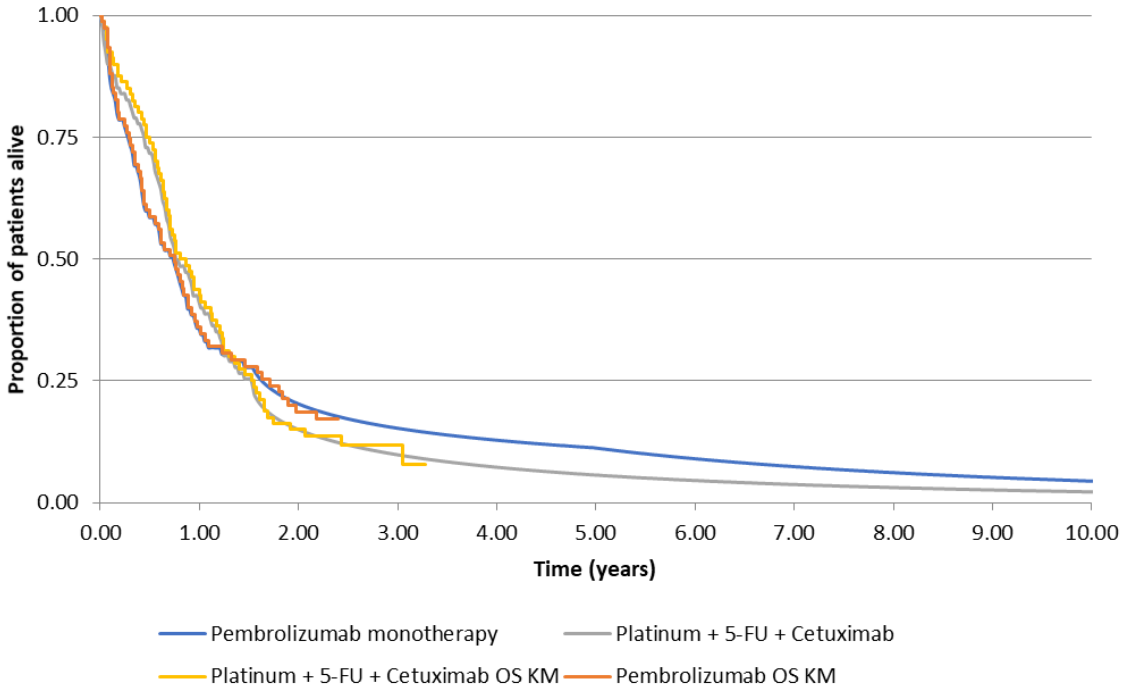
			follow-up study from KN001, titled 'Five-Year Overall Survival for Patients with Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results from the Phase I KN001 Study', we see that the 5-year overall survival rate with pembrolizumab was 23.2% in treatment-naïve patients, providing confidence in the choice of survival extrapolation at year 5 (1). **Figure 1: Pembrolizumab Monotherapy with 5-year Treatment Waning (oral Cavity Subgroup)**  **Figure 2: Pembrolizumab Combination Therapy with 5-year Treatment Waning (Oral Cavity Subgroup)**	although a longer duration of treatment benefit is biologically plausible, the duration is currently unknown. This is because there is no evidence to support treatment effect duration beyond 5 years in HNSCC, and because the treatment effect duration from another disease area could not be transferred to HNSCC because of differences in the physiology and genetic profile of the tumours. The committee concluded that assuming a 5-year treatment effect duration was more appropriate, and consistent with the previous HNSCC immunotherapy appraisal. Please see section 3.10 of the FAD for a summary of the committee's discussion.

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			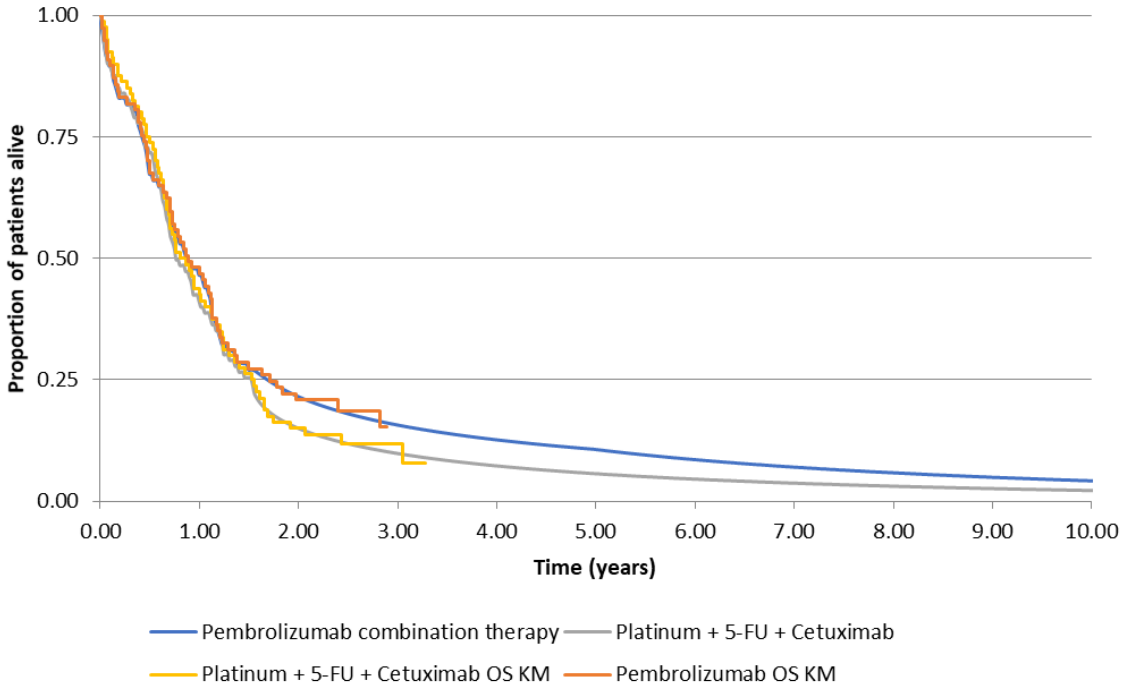 The Log-normal was the best fitting curve for the cetuximab plus platinum-based chemotherapy arm; however, it overestimates 5-year overall survival compared to the 5-year data from the EXTREME trial (2). This data from the EXTREME study indicated 5-year overall survival of 2.9% (Table 27, Appendix 4); the Weibull curve provided a better fit to the observed data (5.8%) and was therefore selected for the cetuximab + platinum + 5-FU arm. MSD would like to note that the applicability of the EXTREME trial is limited by the fact that the EXTREME trial looked at all recurrent/metastatic squamous cell head and neck cancer patients, where as the estimates presented by MSD are for the oral cavity subgroup alone. The NICE TSD 14 states that “Similar types of models (with ‘type’ defined as the same parametric distribution) should be used for the different treatment arms unless there is strong evidence to suggest an alternative is more plausible”. Such long-term clinical evidence from the EXTREME study would indicate that the Weibull is a more appropriate choice. The choice of varying curves was also supported through clinical validation. Such a methodology has already been utilised in previous pembrolizumab appraisals, such as TA600 (3). MSD has applied the 5-year treatment waning as requested by the committee. However, clinicians questioned	

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			by NICE stated that "the duration of treatment effect with pembrolizumab or other IO agents are likely to be 5 years or more". Additionally, in the ACD, clinical experts expressed "that conceptually it was possible that pembrolizumab's treatment effect could last as long as 10 years because immunotherapies such as pembrolizumab have a different mechanism to cytotoxic therapies". A statement of similar effect was made by the clinical expert as part of TA490 appraisal; Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy. The statement read "I believe that the majority of patients who enter the plateau phase will continue to enjoy the health benefits (including out to 5 – 10 years)". A 5-year treatment waning effect therefore represents a highly conservative assumption and produces long-term survival estimates well below those expected by clinicians. **Non-oral Cavity Subgroup** In both the pembrolizumab monotherapy and combination therapy regimens, the Log-normal gave the best goodness-of-fit as can be seen in Table 32 and Table 33. With the 5-year treatment waning effect applied this results in a 5- and 10-year overall survival of 17.0% and 2.5% respectively for pembrolizumab monotherapy regimen. With the 5-year treatment waning effect applied this results in a 5- and 10-year overall survival of 22.9% and 3.4% respectively for pembrolizumab combination therapy (Table 34). Clinical expert feedback to MSD regarding overall survival was in the range of 14 – 19% at 5 years, hence when considering external validation, this is a highly conservative survival extrapolation for pembrolizumab monotherapy and combination therapy. Making use of 5-year follow-up data from other pembrolizumab clinical studies, as referenced in the long-term follow-up study from KN001, titled 'Five-Year Overall Survival for Patients with Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results from the Phase I KN001 Study', we see that the 5-year overall survival rate with pembrolizumab was 23.2% in treatment-naïve patients, providing confidence in the choice of survival extrapolation at year 5 (1). **Figure 3: Pembrolizumab Monotherapy with 5-year Treatment Waning (Non-oral Cavity Subgroup)**	

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			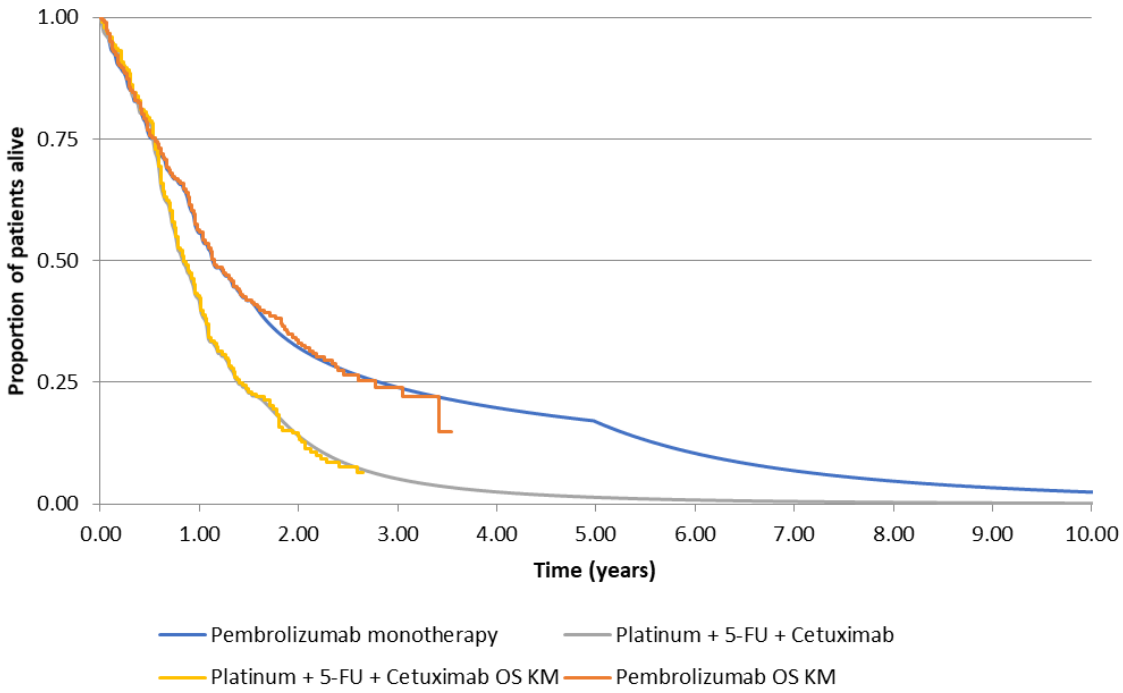 **Figure 4: Pembrolizumab Combination Therapy with 5-year Treatment Waning (Non-oral Cavity Subgroup)**	

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			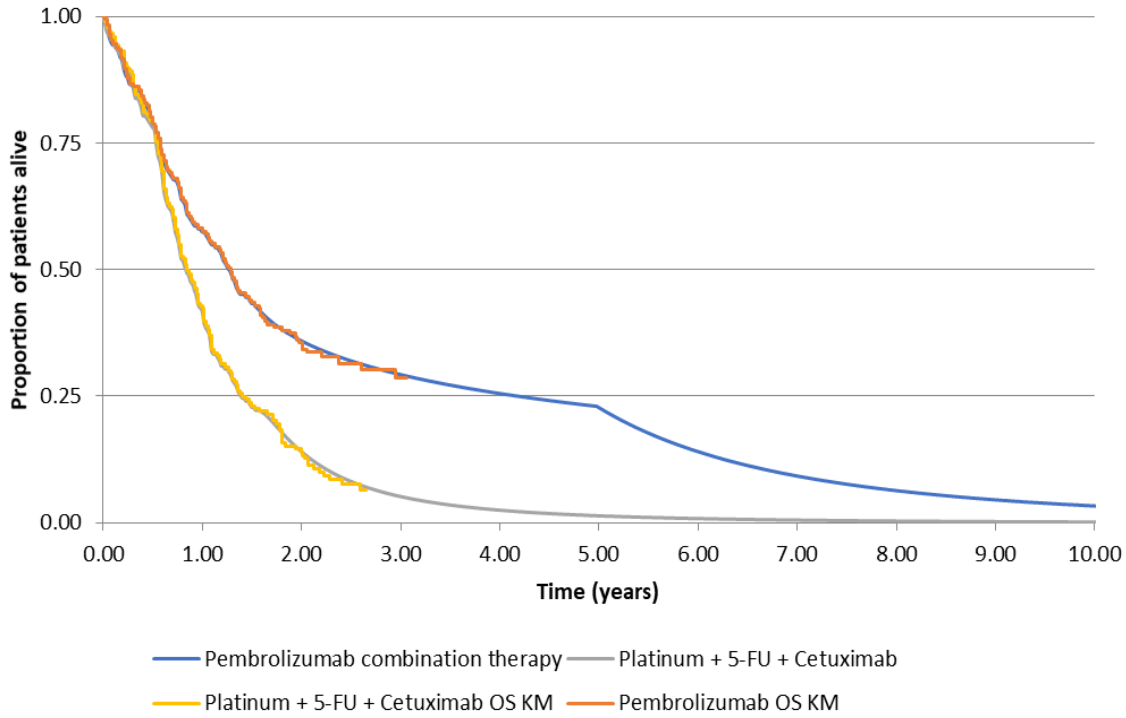 As stated above, 5-year follow-up data from the EXTREME study was used for external validation of the comparator. Referring to Table 27 in Appendix 4, when we compare the curve with the best fit for the comparator arm (Table 35), the Log-normal has a 5-year survival estimate of 1.5% in the (proxy) platinum plus 5-FU arm. This is a good match to the observed 5-year survival in the platinum plus 5-FU arm of 1.7% from the EXTREME follow-up data. Based on these factors, the Log-normal curve was selected for the pembrolizumab monotherapy and combination therapy regimens, as well as the comparator of platinum plus 5-FU, in the non-oral cavity subgroup.	
4	Consultee	Merck Sharp & Dohme	The ACD states the clinical experts were of the opinion the post progression utility value derived from KEYNOTE-048 “was high for people who are normally in very poor health and therefore may be overestimated”. Within the model, time to death is incorporated in the regression analysis, along with the age-related utility decrements. This implies that as patients get closer to death, utility value decreases. MSD believes this should negate any concerns regarding the utility being too high.	Comment noted. The committee accepted the company’s rationale that the original, trial-based post-progression value was consistent with NICE reference

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			Also, the NICE reference case specifies that the "EQ-5D is the preferred measure of health-related quality of life in adults". Additionally, health-related quality of life, or changes in health-related quality of life, should be measured directly by patients (4), and the valuation of health-related quality of life measured by patients (or by their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method. In our submission, MSD has followed the NICE reference case by estimating utilities based on the EQ-5D data collected in KEYNOTE-048 and applying the UK tariff to reflect valuations from the UK general public. This approach fully complies with the NICE reference case and has been previously supported by committees whenever EQ-5D data directly collected from patients in the clinical trials has been available (5-9). To address the committee's concerns however, MSD has used an alternative value for the updated cost-effectiveness results as requested, taken from the results of the systematic literature review. The utility value used in the updated analyses is 0.66, derived from an investigation into the cost-effectiveness of nivolumab for recurrent or metastatic head and neck Cancer (10). The choice of utility value was based on the fact nivolumab has a similar mode of mechanism to pembrolizumab and the literature was in the recurrent or metastatic head and neck cancer setting. Despite these, MSD would like to highlight that this represents a conservative estimate of post- progression utility on the basis that this value comes from Checkmate 141 trial, which investigated the use of nivolumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck **after** platinum chemotherapy, which is a later line of treatment to those patients treated in KEYNOTE-048. This therefore represents a 'sicker' cohort of patients. Additionally, the post-progression utility value reported for patients treated with standard therapy in Checkmate 141 was 0.47 – implying better health-related quality of life for patients treated with an immunotherapy compared to standard chemotherapy. Treatment-independent utility values are used in this economic analysis, potentially further underestimating the cost-effectiveness of pembrolizumab monotherapy and combination therapy, based on the evidence from Checkmate-141. In addition, to support the use of the post-progression utility generated from KEYNOTE-048, there is evidence to show that cancer patients have reported value health states higher than the general population (11-13); this may be as a result of being chronically unwell, and as such these group of patients have more to gain from an improvement in quality of life. In conclusion, patients who have sustained ill health may perceive their improved health state, or a better hypothetical health state, of greater value in comparison to the general population; cancer patients have consistently reported higher patient values when using a time trade off approach (14).	case. But it also noted that EQ-5D data collection in the KEYNOTE-048 trial was subject to informative censoring (see Section 3.12 of the FAD), impacting the validity of both the starting post-progression utility value and time to death utility decrements. Based on the description of the health states in the model, the clinical experts said that the trial-based post-progression utility value was high compared with the quality of life of people who are normally in very poor health, and therefore may be an overestimate. Although some studies suggest people with cancer value health states more highly than the general population, this would not meet the NICE reference case which states that general population health state valuations should be used. MSD has indicated that they correctly applied health state valuations from the UK general population (rather than using valuation from patients). The committee agreed the resulting utility estimate was too high to correctly represent people who are normally in very poor health. Therefore, the committee agreed that a lower utility value, sourced from published literature was more suitable for decision making. See Section 3.12 of the FAD for a summary of the

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<tr><td></td><td></td><td></td><td></td><td>committee's discussions.</td></tr>
<tr><td>5</td><td>Consultee</td><td>Merck Sharp & Dohme</td><td>The ICER results for the oral and non-oral cavity subgroups can be found in Tables 1- 4. The ICER values have been generated making use of the post-progression utility value sourced from literature sources and the overall survival extrapolation curve choices as explained in Content Number 3.

Table 1: Pembrolizumab Monotherapy Oral Cavity Subgroup ICER with Lower Post-Progression Utility Value
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Pembrolizumab monotherapy</td><td>41,309</td><td>1.72</td><td>1.17</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>EXTREME regimen</td><td>60,193</td><td>1.41</td><td>0.98</td><td>-18,883</td><td>0.31</td><td>0.18</td><td>Dominant</td></tr>
<tr><td colspan="8">Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years</td></tr>
</table>
Table 2: Pembrolizumab Combination Therapy Oral Cavity Subgroup ICER with Lower Post-Progression Utility Value
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Pembrolizumab combination therapy</td><td>56,155</td><td>1.80</td><td>1.23</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>EXTREME regimen</td><td>60,193</td><td>1.41</td><td>0.98</td><td>-4,038</td><td>0.39</td><td>0.25</td><td>Dominant</td></tr>
<tr><td colspan="8">Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years</td></tr>
</table>
Table 3: Pembrolizumab Monotherapy Non-oral Cavity Subgroup ICER with Lower Post-Progression Utility Value
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Pembrolizumab monotherapy</td><td>49,304</td><td>2.13</td><td>1.47</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Platinum + 5-FU</td><td>21,913</td><td>1.12</td><td>0.79</td><td>27,391</td><td>1.01</td><td>0.68</td><td>40,121</td></tr>
<tr><td colspan="8">Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years</td></tr>
</table></td><td>Thank you for providing new cost-effectiveness estimates. The committee agreed that Weibull functions are more appropriate for modelling overall survival in the 2 subgroups (see section 3.11 of the FAD). It also agreed that because it is not possible to clearly define distinct patient populations who would be offered pembrolizumab monotherapy or combination therapy, a fully incremental analysis should be used to determine the cost effectiveness of each pembrolizumab regimen (see section 3.13 of the FAD). The committee considered cost-effectiveness results from the analyses which used its preferred assumptions (provided by the ERG) in its decision making. Please see sections 3.16 to 3.18 of the FAD for a summary of these discussions.</td></tr>
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Table 4: Pembrolizumab Combination Therapy Non-Oral Cavity Subgroup ICER with Lower Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	62,676	2.42	1.66	-	-	-	-
Platinum + 5-FU	21,913	1.12	0.79	40,763	1.30	0.87	46,836
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Results including the KN048 post-progression utility value have also been presented in Tables 5 – 8, as these values are more aligned with the recommendations of the NICE methods guide.

Table 5: Pembrolizumab Monotherapy Oral Cavity Subgroup ICER with KN048 Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	41,309	1.72	1.22	-	-	-	-
EXTREME regimen	60,193	1.41	1.01	-18,883	0.31	0.20	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 6: Pembrolizumab Combination Therapy Oral Cavity Subgroup ICER with KN048 Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	56,155	1.80	1.28	-	-	-	-
EXTREME regimen	60,193	1.41	1.01	-4,038	0.39	0.26	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

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Table 7: Pembrolizumab Monotherapy Non-Oral Cavity Subgroup ICER with KN048 Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	49,304	2.13	1.52	-	-	-	-
Platinum + 5-FU	21,913	1.12	0.81	27,391	1.01	0.71	38,358
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 8: Pembrolizumab Combination Therapy Non-Oral Cavity Subgroup ICER with KN048 Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	62,676	2.42	1.72	-	-	-	-
Platinum + 5-FU	21,913	1.12	0.81	40,763	1.30	0.91	44,624
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

An alternative analysis using our fractional polynomial network meta-analysis approach for the comparison of pembrolizumab versus platinum chemotherapy and 5-FU for the subgroup of patients was not carried out. This is because overall survival data (including overall survival Kaplan-Meier curves) specific to the subgroup of patients whose cancer started outside of the oral cavity (the subgroup for which this comparison is relevant) is not available from the EXTREME study. As the network meta-analysis would be driven by the data from KEYNOTE-048 study and EXTREME study for this subgroup, it is not possible to carry out this analysis without this data. As a result, the ERG approach of using non-oral cavity data for cetuximab plus platinum chemotherapy and 5-FU from KEYNOTE- 048 as a proxy for non-oral cavity data for platinum chemotherapy and 5-FU was employed.

As a reminder, the results from the full trial population are presented below in Table 9 and Table 10.

Table 9: Original Submission Pembrolizumab Monotherapy ICER Results- Overall Population

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<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Pembrolizumab monotherapy</td><td>48,945</td><td>2.40</td><td>1.69</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>EXTREME regimen</td><td>51,832</td><td>1.27</td><td>0.91</td><td>-2,886</td><td>1.13</td><td>0.78</td><td>Dominant</td></tr>
<tr><td>Platinum + 5-FU</td><td>20,616</td><td>1.10</td><td>0.78</td><td>28,329</td><td>1.30</td><td>0.91</td><td>31,212</td></tr>
<tr><td colspan="8">Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years</td></tr>
</table>

Table 10: Original Submission Pembrolizumab Combination Therapy ICER Results- Overall Population
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Pembrolizumab combination therapy</td><td>64,414</td><td>3.05</td><td>2.12</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>EXTREME regimen</td><td>52,597</td><td>1.18</td><td>0.85</td><td>11,817</td><td>1.88</td><td>1.28</td><td>9,255</td></tr>
<tr><td>Platinum + 5-FU</td><td>19,652</td><td>0.96</td><td>0.68</td><td>44,762</td><td>2.10</td><td>1.44</td><td>31,070</td></tr>
<tr><td colspan="8">Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years</td></tr>
</table>

MSD would like to highlight that even with the further subgroup analyses, results come to the same conclusion as the overall population; which is, pembrolizumab in both the monotherapy and combination therapy regimens are cost-effective treatments compared to both EXTREME and platinum+5-FU.

A fully incremental analyses was not conducted by MSD. The NICE guide to the methods of technology appraisal states that “the Committee will normally be guided by established practice in the NHS when identifying appropriate comparator(s)”. It goes on to say, “the Committee’s overall decision on whether it is a valid comparator will be guided by whether it is recommended in extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology” (4). Based on these recommendations, MSD do not believe that a full incremental analysis is appropriate as neither pembrolizumab in the monotherapy nor combination therapy regimens is established practice or recommended by NICE, as stated in the NICE methods guide.</td><td></td></tr>
<tr><td>6</td><td>Consultee</td><td>Merck Sharp & Dohme</td><td>The rationale given at the end of section 1 of the Appraisal Consultation Document for why the committee made their recommendations, which determined the nature of the requests for further clarification and</td><td>Comment noted. The current guide to the methods of</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
			analyses from the company listed in section 1.2, is based on the committee's assertion as stated in section 3.6 of the Appraisal Consultation Document that: "because current treatment options are different for cancer that started inside or outside the oral cavity in the NHS in England (see section 3.3), it was appropriate to consider the clinical effectiveness of pembrolizumab in the 2 population subgroups: cancer starting inside or outside the oral cavity". However, this reasoning is based on the assumption that the clinical effectiveness of pembrolizumab (both as monotherapy and in combination with platinum-based chemotherapy plus 5-fluorouracil) or its relevant comparators (cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil or just platinum-based chemotherapy plus 5-fluorouracil) differ depending on the site of tumour origin (specifically, in the oral cavity versus outside of the oral cavity), which is an assumption that is not supported by evidence. While the site of tumour origin is a determinant of which treatment a patient receives in the NHS in England, this is an artificial determinant not based on scientific clinical rationale (as pointed out during technical engagement, documented on pages 681-682 of the Committee papers PDF file). In short, this assumption/determinant is based solely on a set of underpowered statistically invalid subgroup analyses presented as part of the NICE technology appraisal of cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (TA172/TA473) where a set of 40 independent subgroup analyses testing at the 5% significance level were presented (shown in section 6.4 pages 46-48 of Merck Serono's submission for TA172), that did not actually include patients whose tumour originated outside of the oral cavity as a distinct subgroup for analysis. To contextualise how statistically invalid the results of these analyses are, a major publication on the topic of reporting of subgroup analyses in clinical trials (https://doi.org/10.1056/NEJMsr077003) points out that: "When multiple subgroup analyses are performed, the probability of a false positive finding can be substantial. For example, if the null hypothesis is true for each of 10 independent tests for interaction at the 0.05 significance level, the chance of at least one false positive result exceeds 40%" Accordingly, when 40 independent subgroup analyses testing at the 5% significance level are carried out, the chance of misleading false positive results would be considerably greater than 40% such that any of the individual results in this set of analyses loses scientifically rigorous informative value. The compromised nature of the validity of these subgroup analyses and consequently their unsuitability for use in decision-making was specifically pointed out in the publication for the pivotal trial that formed the foundation of the TA172/TA473 evidence base (https://doi.org/10.1056/NEJMoa0802656), which stated that: "There was a significant interaction with the primary tumor site, but because of repeated testing, this result could be due to chance. Such subgroup analyses must be interpreted cautiously; the results do not allow us to state with certainty that some groups did not benefit or to speculate on the degree of benefit." Furthermore, NICE's own guide to the methods of technology appraisal state that, with regard to the analysis	technology appraisal states that: • "The characteristics of patients in the subgroup should be clearly defined and should preferably be identified on the basis of an expectation of differential clinical or cost effectiveness because of known, biologically plausible mechanisms, social characteristics or other clearly justified factors. " • "Consideration of subgroups based on differential cost may be appropriate in some circumstances; for example, if the cost of managing a particular complication of treatment is known to be different in a specific subgroup". Current treatment options in the NHS in England are different for cancer that started inside or outside the oral cavity, because cetuximab is only recommended for people whose cancer started inside the oral cavity (TA473). Therefore the relevant comparators and their costs are different for cancer that started inside and outside the oral cavity, and the cost-effectiveness needs to be considered separately for each subgroup. The committee also noted that the relative efficacy of pembrolizumab

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			of data for patient subgroups (section 5.10): Section 5.10.2: There should be a clear justification and, if appropriate, biological plausibility for the definition of the patient subgroup and the expectation of a differential effect. Post hoc data 'dredging' in search of subgroup effects is to be avoided and will be viewed sceptically. Section 5.10.7: The evidence supporting biological or clinical plausibility for a subgroup effect should be fully documented, including details of statistical analysis. Therefore, in the absence of biological or clinical plausibility for a subgroup effect based on site of tumour origin for either pembrolizumab or the comparator (it is specifically noted in section 4.3 of the TA172 final appraisal determination document that "the specialists were not aware of any biological reason for cetuximab to be more clinically effective in oral cavity tumours"), the set of 40 analyses in search of subgroup effects used by the committee to justify the rationale for its recommendation, and the post hoc subgroup analyses requested now by the committee as part of this Appraisal Consultation Document, contradict these guidance. In addition, section 5.10.11 of the methods guide also states that: Types of subgroups that are not considered relevant are those based solely on the following factors: subgroups based solely on differential treatment costs for individuals according to their social characteristics As evidence for differences in the treatment effect of interventions in patients whose tumour originated in the oral cavity versus in patients whose tumour originated outside of the oral cavity is lacking, while there is evidence that shows there are distinct differences in the social characteristics between these patient groups (https://doi.org/10.1002/ijc.31416), and there are differential treatment costs between these patient groups in the NHS in England (as cetuximab in addition to platinum-based chemotherapy and 5-fluorouracil is currently only recommended by NICE for the treatment of the subgroup of patients whose cancer originated in the oral cavity), it is clear that the recommendations and requests from the committee in this Appraisal Consultation Document also contradict this section of guidance. Therefore, it is not appropriate for the committee to make their recommendation in this appraisal based on an underlying assumption that is flawed/unsupported by evidence to this degree, in a way that contradicts NICE's own published guidance on the processes and methods for technology appraisal.	(monotherapy or in combination) may be different in the 2 subgroups, which could be because of the differences in the efficacy of pembrolizumab or cetuximab combination therapy, or because the trial was not designed to analyse differences between the subgroups. The committee noted that TA473 suggests that cetuximab with platinum chemotherapy and 5-FU might be more effective in people whose cancer started inside the oral cavity. The committee also noted that the relative efficacy of pembrolizumab (monotherapy or in combination) may be different in the 2 subgroups, which could be because of the differences in the efficacy of pembrolizumab or cetuximab combination therapy, or because the trial was not designed to analyse differences between the subgroups. Therefore, the committee's decision to use subgroup data was based on differences in treatments available to each subgroup (and their costs), possible differences in the relative effectiveness of pembrolizumab against cetuximab combination therapy, and possible differences in the relative

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				effectiveness of cetuximab combination therapy against chemotherapy alone, as shown in previous appraisals. It was not because of the differential treatment costs for individuals according to their social characteristics. The committee concluded that clinical effectiveness should be considered separately for cancer starting inside or outside the oral cavity (see section 3.6 of the FAD for details).
7	Consultee	Merck Sharp & Dohme	With regard to the following statements in section 3.7 of the ACD: "The ERG explained that it was concerned about the analysis's validity because the company did not consider the plausibility of the hazard ratios estimated by the fractional polynomial model. The company did not say how the 2 categories of fractional polynomial models were assessed." This is not correct as MSD provided descriptions both of how the plausibility of the hazard ratios estimated by the fractional polynomial model were considered and how the 2 categories of fractional polynomial models were assessed as part of the technical engagement response form, as documented on page 12 of 38 of the technical engagement response from Merck Sharp & Dohme, shown on page 687 of 816 of the Committee papers PDF file.	Comment noted. The ERG has confirmed that the methods used in the network meta-analysis were appropriate. This sentence has been removed from the FAD. See section 3.8 of the FAD for a summary of committee's discussions about the indirect treatment comparison of pembrolizumab with platinum chemotherapy and 5-FU.
8	Consultee	Merck Sharp & Dohme	With regard to the following statement in section 3.7 of the ACD: "The committee noted the results from the 2 approaches and considered that the company's approach may overestimate the effectiveness of pembrolizumab (monotherapy and in combination)" It should be noted that that MSD's approach that uses the fractional polynomial network meta-analysis is in fact more likely to *underestimate* the true effectiveness of pembrolizumab (monotherapy and in combination) versus platinum chemotherapy and 5-FU, as was explained on page 12 of 38 of the technical engagement response from Merck Sharp & Dohme, shown on page 687 of 816 of the Committee papers PDF file.	Comment noted. The ERG has confirmed that the methods used in the network meta-analysis were appropriate. But their preferred approach was to use the Kaplan–Meier data from the cetuximab combination therapy arm of KEYNOTE-048 as a proxy for chemotherapy alone for people whose cancer started outside the oral cavity (see section 3.8 of the FAD). Because the company's network meta-analysis was not possible for

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				the subgroups, and the company used the ERGs preferred approach in the subgroup analyses, the committee did not consider this issue further. But it acknowledged the ERG's approach may overestimate the efficacy of chemotherapy alone. See section 3.8 of the FAD for a summary of committee's discussions about the indirect treatment comparison of pembrolizumab with chemotherapy alone.
9	Consultee	NCRI-ACP-RCP-RCR	Our experts are concerned that this recommendation is not a sound and suitable basis for guidance to the NHS due to the recommendation being based upon the premise that the use of cetuximab in non-oral cavity HNSCC does not reflect clinical practice in the NHS in England. The restriction on the use of cetuximab to the oral cavity subgroup was a health economic decision made by NICE based on a sub-group analysis of the original study of chemotherapy with or without cetuximab (Vermorken, NEJM, 2008). The rationale was that a sub-group analysis of the whole group treated with chemotherapy + cetuximab showed that the greatest survival gains were seen in oral cavity group -and the improvements in survival with cetuximab in the non-oral cavity group did not reach statistical significance. This restriction to the use of cetuximab to oral cavity has not been adopted internationally and as the study was required to have international recruitment, the restriction of cetuximab to the oral-cavity subgroup would have been considered unethical in all other health care systems outside the NHS in England as being inferior to the standard of care. As such, it was an appropriate comparator arm in the study design. Moreover, the data from this same sub-group analysis (Vermorken NEJM 2008) did not show any evidence that cetuximab use was associated with worse outcomes. As such, it is not plausible to assume that the inclusion of cetuximab in the comparator arm for patients with non-oral cavity disease would increase the apparent efficacy of the pembrolizumab treated patients in the experimental arms, it would be expected to show the converse.	Comment noted. Current treatment options are different for cancer that started inside or outside the oral cavity in the NHS in England, because cetuximab is only recommended for people whose cancer started inside the oral cavity (TA473). Evidence submitted as part of TA473 also suggests that cetuximab combination therapy might be more effective in people whose cancer started inside the oral cavity (TA473). The committee concluded that clinical and cost-effectiveness should be considered separately for cancer starting inside or outside the oral cavity (see section 3.6 of the FAD for details). The committee acknowledged that assuming equal efficacy of cetuximab combination therapy and chemotherapy alone in the non-oral subgroup might

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				overestimate the efficacy of the latter regimen. But it concluded that this is an acceptable approach for its decision-making based on expert advice (see section 3.8 of the FAD for details).

References

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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	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):	Merck Sharp & Dohme
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Merck Sharp & Dohme does not have any past or current, direct or indirect links to, or funding from, the tobacco industry.
Name of commentator person completing form:	Younan Zhang

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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.
1	A full comparison between treatment arms of baseline patient characteristics for the 2 subgroups (patients whose cancer started inside the oral cavity, and patients whose cancer started outside the oral cavity), of the KEYNOTE-048 study, are provided in Appendix 1 of the appendices document attached to this comments form. **Summary of imbalances in baseline characteristics between treatment arms** Patients whose cancer originated in the oral cavity and with PD-L1 combined positive score (CPS) ≥1 *Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy* Table 1 of Appendix 1 of the appendices document attached to this comments form provides a summary of the baseline characteristics for the comparison of pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1. Given the small size of this sub-population (pembrolizumab monotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]), certain imbalances in baseline characteristics between treatment groups were observed. In cases where imbalances were noted, the magnitude of the imbalances were small, falling within the range of a 5% to 15% difference between treatment groups, with the exception of [redacted] ([redacted] difference across groups). Among continuous variables, the median time from latest platinum therapy was shorter for pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy; however, given the small subgroup of patients with prior platinum therapy (pembrolizumab monotherapy: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]) the influence of any imbalance in this factor on overall survival (OS) could be considered minimal. The following is a summary of the slight imbalances in baseline characteristics identified for the comparison of pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy: • Gender: [redacted] proportion of females in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Geographic region group: [redacted] proportion of patients from North America in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]), and [redacted] proportion from the rest of world (pembrolizumab monotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]). • Smoking status: [redacted] proportion of never smokers in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • PD-L1 tumour positive score (TPS) status ≥50%: [redacted] proportion of patients with strongly positive PD-L1 status (TPS≥50%) in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Disease status: [redacted] proportion of patients with metastatic disease status in the

pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

- Time from latest platinum therapy: Median time from latest platinum therapy was [redacted] for the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]); however, given the small size of the subgroup of patients with prior platinum therapy (pembrolizumab monotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]) the influence of any imbalance in this factor on OS could be considered minimal.

Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Table 2 of Appendix 1 of the appendices document attached to this comments form provides a summary of the baseline characteristics for the comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy arm versus cetuximab in combination with platinum and 5-FU chemotherapy arm in patients with tumours that originated in the oral cavity and with PD-L1 CPS≥1. Given the small size of this sub-population (pembrolizumab in combination with platinum and 5-FU chemotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]), certain imbalances in baseline characteristics between treatment groups were observed. In all cases where imbalances were noted, the magnitude of the imbalances were small, falling within the range of a 5% to 15% difference between treatment groups. Among continuous variables, the median time from latest platinum therapy was shorter for the pembrolizumab in combination with platinum and 5-FU chemotherapy arm versus the cetuximab in combination with platinum and 5-FU chemotherapy arm; however, given the small size of this subgroup of patients with prior platinum therapy (pembrolizumab in combination with platinum and 5-FU chemotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]) the influence of any imbalance in this factor on OS could be considered minimal.

The following is a summary of the slight imbalances in baseline characteristics identified for the comparison of the pembrolizumab in combination with platinum and 5-FU chemotherapy arm versus the cetuximab in combination with platinum and 5-FU chemotherapy arm:

- Gender: [redacted] proportion of females in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

- Age: [redacted] proportion of patients with age ≥65 years in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

- Geographic region group: [redacted] proportion of patients from North America in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

- Smoking status: [redacted] proportion of current smokers in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

- ECOG: [redacted] proportion of patients with ECOG 0 in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

- PD-L1 TPS≥50%: [redacted] proportion of patients with strongly positive PD-L1 status (TPS≥50%) in

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the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

- PD-L1 CPS≥20: [redacted] proportion of patients with strongly positive PD-L1 status CPS≥20 in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

- Baseline tumour size (grouping by intention-to-treat [ITT] median): [redacted] proportion with tumour size ≥median in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

- Time from latest platinum therapy: Median time from latest platinum therapy was [redacted] in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]); however, given the small size of the subgroup of patients with prior platinum therapy (pembrolizumab in combination with platinum and 5-FU chemotherapy arm: [redacted]; the cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]) the influence of any imbalance in this factor on OS could be considered minimal.

Patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

Table 3 and Table 4 of Appendix 1 of the appendices document attached to this comments form provide a summary of the baseline characteristics for the comparison of pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, and pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, respectively, in patients whose tumours originated outside of the oral cavity and with PD-L1 CPS≥1. Baseline characteristics were generally well balanced across treatment groups. In cases where imbalances were noted, the magnitude of the imbalances were small, falling within the range of a 5% to 10% difference between treatment groups.

Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy

The following is a summary of the slight imbalances in baseline characteristics identified for the comparison of the pembrolizumab monotherapy arm versus the cetuximab in combination with platinum and 5-FU chemotherapy arm:

- Geographic region group: [redacted] proportion of patients from Europe in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]), and [redacted] proportion from rest of world (pembrolizumab monotherapy arm: [redacted]; cetuximab in combination with platinum and 5-FU chemotherapy arm: [redacted]).

- Time from latest platinum therapy: median time from latest platinum therapy was [redacted] in the pembrolizumab monotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).

Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

The following is a summary of the slight imbalances in baseline characteristics identified for the comparison of the pembrolizumab in combination with platinum and 5-FU chemotherapy arm versus the cetuximab in combination with platinum and 5-FU chemotherapy arm:

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	• Gender: [redacted] proportion of females in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Disease status: [redacted] proportion of patients with metastatic disease status in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]). • Time from latest platinum therapy: median time from latest platinum therapy was [redacted] in the pembrolizumab in combination with platinum and 5-FU chemotherapy arm ([redacted]) versus the cetuximab in combination with platinum and 5-FU chemotherapy arm ([redacted]).
2	Overall survival data (Kaplan-Meier curves, hazard ratios) for the 2 subgroups (patients whose cancer started inside the oral cavity, and patients whose cancer started outside the oral cavity), of the KEYNOTE-048 study, are provided in Appendix 3 of the appendices document attached to this comments form. Subgroup analyses of overall survival to relevant prognostic factors To further understand the potential influence of any slight imbalances on OS, subgroup analyses of OS from the KEYNOTE-048 study according to each relevant prognostic factor were conducted separately within the population of patients with tumours that originated in the oral cavity and PD-L1 CPS≥1 (Figures 1 and Figure 2 in Appendix 2 of the appendices document attached to this comments form), and within the population of patients with tumours that originated outside of the oral cavity and PD-L1 CPS≥1 (Figures 3 and Figure 4 pf the appendices document attached to this comments form). As shown in the forest plots for both the comparison of pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, and pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, within each sub-population, analyses of OS according to each relevant prognostic factor were consistent with the primary findings, with all 95% confidence intervals in the subgroup analyses overlapping the 95% confidence interval of the hazard ratio of the primary analysis. Therefore, given that the relative treatment effects on OS did not appear to differ by the baseline characteristics that were found to be slightly imbalanced, there is no evidence to suggest that approaches to adjust for the slight imbalances in certain prognostic factors would materially impact the OS results. Methodological options considered for adjusting survival curves for potential imbalances in prognostic factors between treatment arms The committee has recommended that NICE requests an adjustment of the oral cavity and non-oral cavity OS Kaplan-Meier curves and hazard ratios for imbalances in baseline patient characteristics in the subgroups and further advised to not restrict it to just the covariates that are unbalanced, referencing NICE Decision Support Unit Technical Support Document 17. The reference document provides guidance on methods used with observational data, and while it does provide some guidance on adjustments for prognostic factors on outcomes (regression adjustment, multivariate regression, propensity score, or instrumental variables) within observational data, there is minimal discussion within this document related to case-control studies and no discussion related specifically to the adjustment of survival data within economic models. We have identified two key methods that one can use, within an economic model using survival curves, in order to address issues related to confounding bias: the average covariate method and corrected group prognostic method. 1. The first method, the average covariate method, provides covariate adjusted Kaplan-Meier curves. This method is ideally suited to predicting survival in a particular subgroup. However,

importantly, it assumes the variables that are adjusted are continuous covariates. This adjusted curve is designed to represent a "hypothetical average individual."

2. The second method, the corrected group prognostic method, is a "bottom- up group average approach" (https://doi.org/10.1093/oxfordjournals.aje.a008670, https://doi.org/10.1001/jama.286.12.1494, https://doi.org/10.1007/s10985-008-9098-9). One develops survival curves using the estimated coefficients from the Cox proportional hazards model and then calculates a weighted survival average curve combining the individually estimated curves. This method is ideally suited to predicting survival in a heterogenous group of individuals. It also assumes that the variables being adjusted are categorical covariates (or recoded continuous variables). This curve represents a grouped population average.

Both adjustment methods have been previously presented to NICE as part of a technology appraisal for lenvatinib for untreated advanced hepatocellular carcinoma (NICE appraisal ID1089 resulting in NICE technology appraisal guidance TA551), with the limitations of both methods noted. The adjustments were conducted to address imbalances for key baseline characteristics. It is worth noting that in the case of the REFLECT trial that although two different adjustments were presented and acknowledging the imbalances, the committee acknowledged that the data within the trial itself was relevant to clinical practice (https://www.nice.org.uk/guidance/ta551/chapter/3-Committee-discussion):

> "The company highlighted that in REFLECT, more people in the lenvatinib group had alpha-fetoprotein levels of 200 ng/ml or above compared with the sorafenib group, and there were differences in the pre-existing liver conditions associated with hepatocellular carcinoma (hepatitis C, hepatitis B or alcohol) across the 2 groups. The company explained that these variables were not included as randomisation stratification factors. It considered that these imbalances in baseline characteristics may affect the treatment benefit seen with lenvatinib because they were potentially important prognostic factors. However, the clinical experts explained that a similar treatment benefit was likely regardless of pre-existing liver conditions."

In the case of prognostic variable adjustment within specific subgroups of the KEYNOTE-048 study, at first pass it seems that between the two methods, the average covariate method would be most appropriate and perhaps the most straight forward method to more carefully examine the individual subgroups, especially given the committee's request to adjust multiple variables. However, upon careful review of potential variables of concern, within the subgroups, it appears that additional adjustment within this case-control trial could introduce greater uncertainty and perhaps bias within the model for reasons further specified in the following section.

Consideration of confounding among prognostic variables in KEYNOTE-048

When considering specific variables for adjustment, it is important to first understand which of these variables are causally related to the disease. If the purported confounders are in fact causally related to the disease, then it is, of course, appropriate to use them as adjustment variables. If this step is carelessly done and unnecessary confounders are incorporated into the analysis two things could occur:

1. Extra variability would be introduced into the estimates of risk.

2. Bias could be introduced by (unintentionally or intentionally) selecting confounders that most reduce the disease-exposure association.

Upon examination of the forest plots of the subgroup analyses of overall survival to relevant prognostic factors described previously (Figures 1-4 of Appendix 2 of the appendices document attached to the comments form), all of the variables for both the oral cavity primary tumour and non-oral cavity primary tumour analyses had overlapping confidence intervals and no obvious patterns

	were seen between the prognostic factors when examining both the different treatment groups as well as the different subgroups. If some of the more extreme examples are examined, for example, [redacted] in the oral cavity primary tumour CPS≥1 group of the pembrolizumab in combination with platinum and 5-FU chemotherapy treatment arm, it visually has the largest difference among the prognostic factors (Figure 1), recognising that the confidence intervals do overlap and the total n for each arm is [redacted] and [redacted] for the pembrolizumab in combination with platinum and 5-FU chemotherapy treatment arm and the cetuximab in combination with platinum and 5-FU chemotherapy arm, respectively. However, when one then looks at the same subgroup (oral cavity primary tumour CPS≥1) for pembrolizumab monotherapy arm compared to the cetuximab in combination with platinum and 5-FU chemotherapy arm, this imbalance is absent (Figure 2). This is also not an obvious variable of interested among the non-oral cavity primary tumour patients (Figures 3-4). This indicates that [redacted] is likely not an appropriate prognostic factor to adjust for and if adjusted, could potentially insert bias and variability. Upon careful review, no prognostic factors were identified that would be of obvious value to adjust for, especially given that this is a case-control study. For these reasons, OS adjustments for imbalances in baseline characteristics in the oral cavity primary tumour and non-oral cavity primary tumour subgroups of the KEYNOTE-048 trial have not been applied.
3	The NICE DSU Technical Support Document 14 was used as the basis for extrapolation curve selection. The methods employed were: • AIC/BIC test (statistical test) • External data validation • Clinical validity **Oral Cavity Subgroup** The statistical test showed the Log-normal to have the second-best ranking in the pembrolizumab monotherapy and combination therapy regimens as can be seen in Table 25 in Appendix 4. With the five-year treatment waning effect applied, this results in a 5- and 10-year overall survival of 11.3% and 4.5% respectively for pembrolizumab monotherapy. With the five-year treatment waning effect applied this results in a 5- and 10-year overall survival of 10.8% and 4.3% respectively for pembrolizumab combination therapy as can be seen in Table 31. Clinical expert feedback to MSD on overall survival was in the range of 14 – 19% at 5 years; hence, when considering external validation, this is a highly conservative survival extrapolation for pembrolizumab monotherapy and combination therapy. Graphs representing the overall survival in both regimens can be found below. Making use of 5-year follow-up data from other pembrolizumab clinical studies, as referenced in the long-term follow-up study from KN001, titled 'Five-Year Overall Survival for Patients with Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results from the Phase I KN001 Study', we see that the 5-year overall survival rate with pembrolizumab was 23.2% in treatment-naïve patients, providing confidence in the choice of survival extrapolation at year 5 (1). **Figure 1: Pembrolizumab Monotherapy with 5-year Treatment Waning (oral Cavity Subgroup)**

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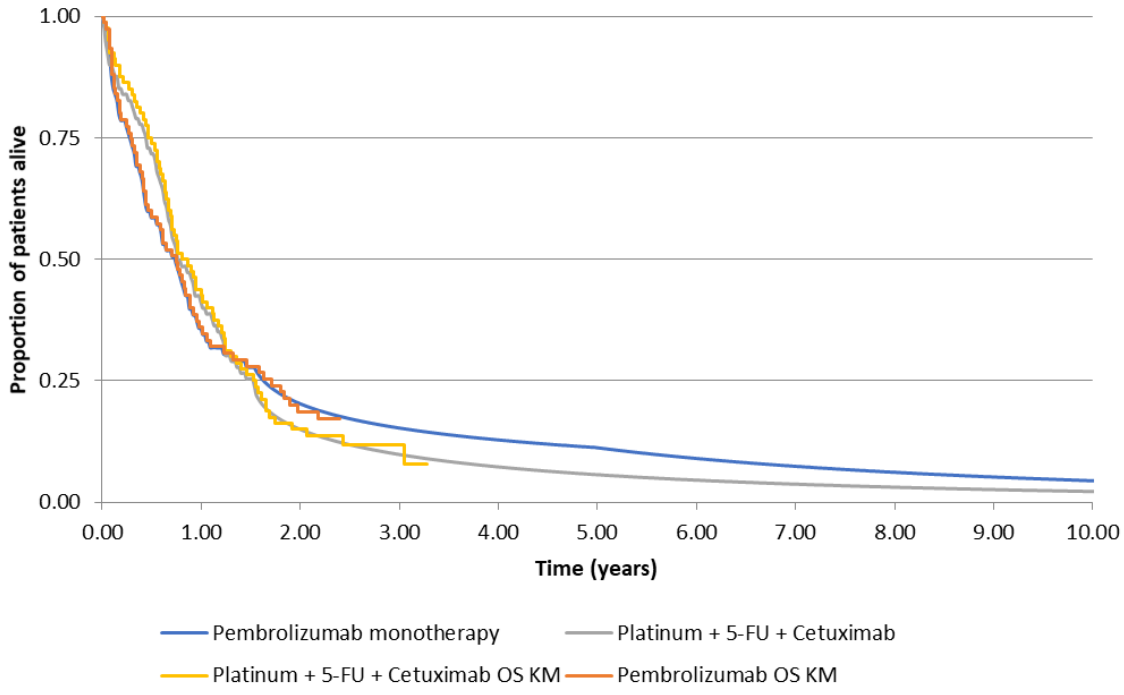
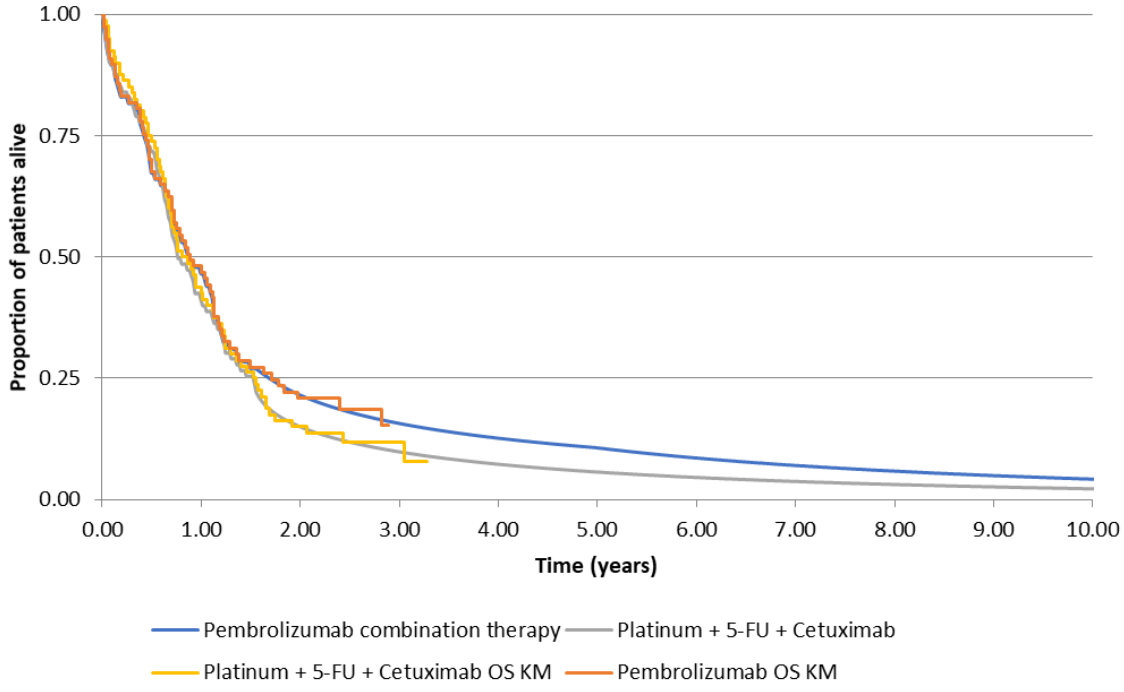


Figure 2: Pembrolizumab Combination Therapy with 5-year Treatment Waning (Oral Cavity Subgroup)



The Log-normal was the best fitting curve for the cetuximab plus platinum-based chemotherapy arm; however, it overestimates 5-year overall survival compared to the 5-year data from the EXTREME

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	trial (2). This data from the EXTREME study indicated 5-year overall survival of 2.9% (Table 27, Appendix 4); the Weibull curve provided a better fit to the observed data (5.8%) and was therefore selected for the cetuximab + platinum + 5-FU arm. MSD would like to note that the applicability of the EXTREME trial is limited by the fact that the EXTREME trial looked at all recurrent/metastatic squamous cell head and neck cancer patients, where as the estimates presented by MSD are for the oral cavity subgroup alone. The NICE TSD 14 states that "Similar types of models (with 'type' defined as the same parametric distribution) should be used for the different treatment arms unless there is strong evidence to suggest an alternative is more plausible". Such long-term clinical evidence from the EXTREME study would indicate that the Weibull is a more appropriate choice. The choice of varying curves was also supported through clinical validation. Such a methodology has already been utilised in previous pembrolizumab appraisals, such as TA600 (3). MSD has applied the 5-year treatment waning as requested by the committee. However, clinicians questioned by NICE stated that "the duration of treatment effect with pembrolizumab or other IO agents are likely to be 5 years or more". Additionally, in the ACD, clinical experts expressed "that conceptually it was possible that pembrolizumab's treatment effect could last as long as 10 years because immunotherapies such as pembrolizumab have a different mechanism to cytotoxic therapies". A statement of similar effect was made by the clinical expert as part of TA490 appraisal; Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy. The statement read "I believe that the majority of patients who enter the plateau phase will continue to enjoy the health benefits (including out to 5 – 10 years)". A 5-year treatment waning effect therefore represents a highly conservative assumption and produces long-term survival estimates well below those expected by clinicians. **Non-oral Cavity Subgroup** In both the pembrolizumab monotherapy and combination therapy regimens, the Log-normal gave the best goodness-of-fit as can be seen in Table 32 and Table 33. With the 5-year treatment waning effect applied this results in a 5- and 10-year overall survival of 17.0% and 2.5% respectively for pembrolizumab monotherapy regimen. With the 5-year treatment waning effect applied this results in a 5- and 10-year overall survival of 22.9% and 3.4% respectively for pembrolizumab combination therapy (Table 34). Clinical expert feedback to MSD regarding overall survival was in the range of 14 – 19% at 5 years, hence when considering external validation, this is a highly conservative survival extrapolation for pembrolizumab monotherapy and combination therapy. Making use of 5-year follow-up data from other pembrolizumab clinical studies, as referenced in the long-term follow-up study from KN001, titled 'Five-Year Overall Survival for Patients with Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results from the Phase I KN001 Study', we see that the 5-year overall survival rate with pembrolizumab was 23.2% in treatment-naïve patients, providing confidence in the choice of survival extrapolation at year 5 (1). **Figure 3: Pembrolizumab Monotherapy with 5-year Treatment Waning (Non-oral Cavity Subgroup)**

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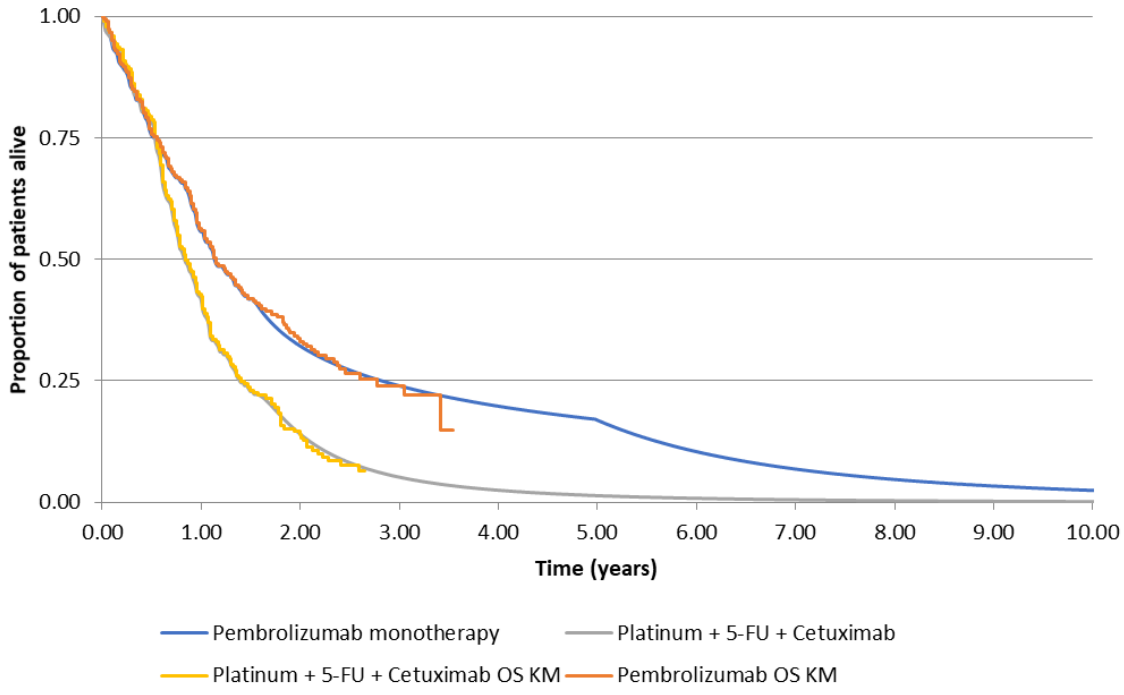
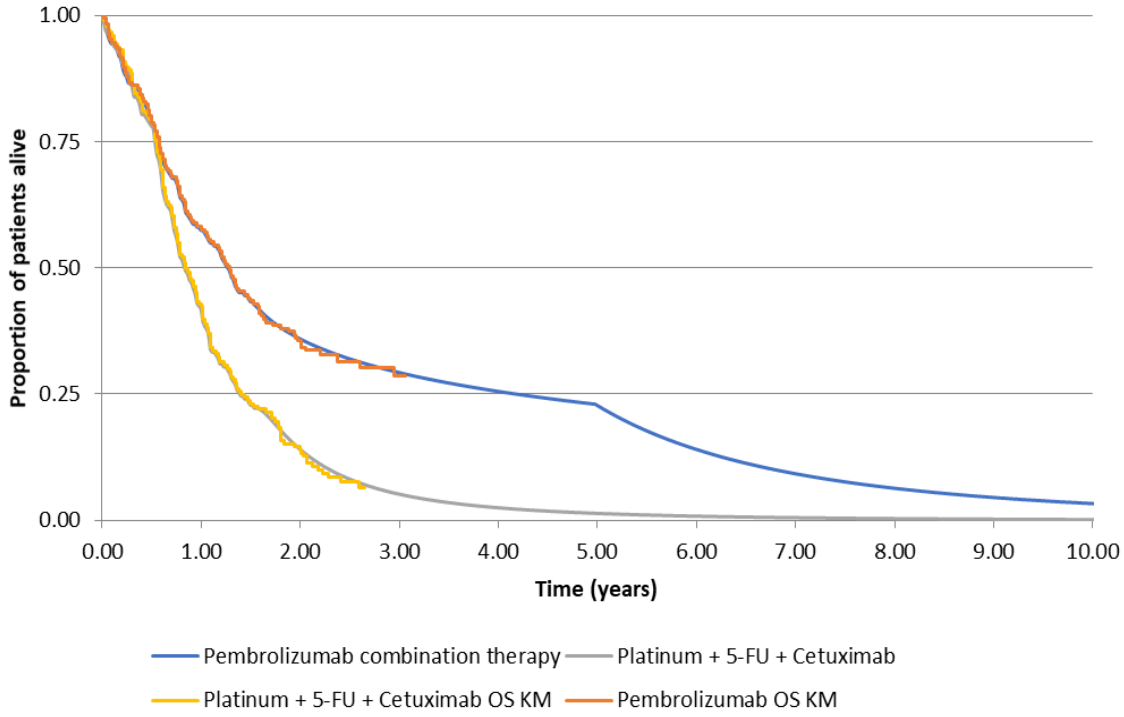


Figure 4: Pembrolizumab Combination Therapy with 5-year Treatment Waning (Non-oral Cavity Subgroup)



As stated above, 5-year follow-up data from the EXTREME study was used for external validation of the comparator. Referring to Table 27 in Appendix 4, when we compare the curve with the best fit for

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	the comparator arm (Table 35), the Log-normal has a 5-year survival estimate of 1.5% in the (proxy) platinum plus 5-FU arm. This is a good match to the observed 5-year survival in the platinum plus 5-FU arm of 1.7% from the EXTREME follow-up data. Based on these factors, the Log-normal curve was selected for the pembrolizumab monotherapy and combination therapy regimens, as well as the comparator of platinum plus 5-FU, in the non-oral cavity subgroup.
4	The ACD states the clinical experts were of the opinion the post progression utility value derived from KEYNOTE-048 "was high for people who are normally in very poor health and therefore may be overestimated". Within the model, time to death is incorporated in the regression analysis, along with the age-related utility decrements. This implies that as patients get closer to death, utility value decreases. MSD believes this should negate any concerns regarding the utility being too high. Also, the NICE reference case specifies that the "EQ-5D is the preferred measure of health-related quality of life in adults". Additionally, health-related quality of life, or changes in health-related quality of life, should be measured directly by patients (4), and the valuation of health-related quality of life measured by patients (or by their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method. In our submission, MSD has followed the NICE reference case by estimating utilities based on the EQ-5D data collected in KEYNOTE-048 and applying the UK tariff to reflect valuations from the UK general public. This approach fully complies with the NICE reference case and has been previously supported by committees whenever EQ-5D data directly collected from patients in the clinical trials has been available (5-9). To address the committee's concerns however, MSD has used an alternative value for the updated cost-effectiveness results as requested, taken from the results of the systematic literature review. The utility value used in the updated analyses is 0.66, derived from an investigation into the cost-effectiveness of nivolumab for recurrent or metastatic head and neck Cancer (10). The choice of utility value was based on the fact nivolumab has a similar mode of mechanism to pembrolizumab and the literature was in the recurrent or metastatic head and neck cancer setting. Despite these, MSD would like to highlight that this represents a conservative estimate of post-progression utility on the basis that this value comes from Checkmate 141 trial, which investigated the use of nivolumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck **after** platinum chemotherapy, which is a later line of treatment to those patients treated in KEYNOTE-048. This therefore represents a 'sicker' cohort of patients. Additionally, the post-progression utility value reported for patients treated with standard therapy in Checkmate 141 was 0.47 – implying better health-related quality of life for patients treated with an immunotherapy compared to standard chemotherapy. Treatment-independent utility values are used in this economic analysis, potentially further underestimating the cost-effectiveness of pembrolizumab monotherapy and combination therapy, based on the evidence from Checkmate-141. In addition, to support the use of the post-progression utility generated from KEYNOTE-048, there is evidence to show that cancer patients have reported value health states higher than the general population (11-13); this may be as a result of being chronically unwell, and as such these group of patients have more to gain from an improvement in quality of life. In conclusion, patients who have sustained ill health may perceive their improved health state, or a better hypothetical health state, of greater value in comparison to the general population; cancer patients have consistently reported higher patient values when using a time trade off approach (14).
5	The ICER results for the oral and non-oral cavity subgroups can be found in Tables 1- 4. The ICER values have been generated making use of the post-progression utility value sourced from literature sources and the overall survival extrapolation curve choices as explained in Content Number 3.

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Table 1: Pembrolizumab Monotherapy Oral Cavity Subgroup ICER with Lower Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	41,309	1.72	1.17	-	-	-	-
EXTREME regimen	60,193	1.41	0.98	-18,883	0.31	0.18	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 2: Pembrolizumab Combination Therapy Oral Cavity Subgroup ICER with Lower Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	56,155	1.80	1.23	-	-	-	-
EXTREME regimen	60,193	1.41	0.98	-4,038	0.39	0.25	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 3: Pembrolizumab Monotherapy Non-oral Cavity Subgroup ICER with Lower Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	49,304	2.13	1.47	-	-	-	-
Platinum + 5-FU	21,913	1.12	0.79	27,391	1.01	0.68	40,121

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 4: Pembrolizumab Combination Therapy Non-Oral Cavity Subgroup ICER with Lower Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	62,676	2.42	1.66	-	-	-	-
Platinum + 5-FU	21,913	1.12	0.79	40,763	1.30	0.87	46,836

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Results including the KN048 post-progression utility value have also been presented in Tables 5 – 8, as these values are more aligned with the recommendations of the NICE methods guide.

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Table 5: Pembrolizumab Monotherapy Oral Cavity Subgroup ICER with KN048 Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	41,309	1.72	1.22	-	-	-	-
EXTREME regimen	60,193	1.41	1.01	-18,883	0.31	0.20	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 6: Pembrolizumab Combination Therapy Oral Cavity Subgroup ICER with KN048 Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	56,155	1.80	1.28	-	-	-	-
EXTREME regimen	60,193	1.41	1.01	-4,038	0.39	0.26	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 7: Pembrolizumab Monotherapy Non-Oral Cavity Subgroup ICER with KN048 Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	49,304	2.13	1.52	-	-	-	-
Platinum + 5-FU	21,913	1.12	0.81	27,391	1.01	0.71	38,358
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 8: Pembrolizumab Combination Therapy Non-Oral Cavity Subgroup ICER with KN048 Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	62,676	2.42	1.72	-	-	-	-
Platinum + 5-FU	21,913	1.12	0.81	40,763	1.30	0.91	44,624
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

An alternative analysis using our fractional polynomial network meta-analysis approach for the

comparison of pembrolizumab versus platinum chemotherapy and 5-FU for the subgroup of patients was not carried out. This is because overall survival data (including overall survival Kaplan-Meier curves) specific to the subgroup of patients whose cancer started outside of the oral cavity (the subgroup for which this comparison is relevant) is not available from the EXTREME study. As the network meta-analysis would be driven by the data from KEYNOTE-048 study and EXTREME study for this subgroup, it is not possible to carry out this analysis without this data. As a result, the ERG approach of using non-oral cavity data for cetuximab plus platinum chemotherapy and 5-FU from KEYNOTE- 048 as a proxy for non-oral cavity data for platinum chemotherapy and 5-FU was employed.

As a reminder, the results from the full trial population are presented below in Table 9 and Table 10.

Table 9: Original Submission Pembrolizumab Monotherapy ICER Results- Overall Population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	48,945	2.40	1.69	-	-	-	-
EXTREME regimen	51,832	1.27	0.91	-2,886	1.13	0.78	Dominant
Platinum + 5-FU	20,616	1.10	0.78	28,329	1.30	0.91	31,212
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 10: Original Submission Pembrolizumab Combination Therapy ICER Results- Overall Population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	64,414	3.05	2.12	-	-	-	-
EXTREME regimen	52,597	1.18	0.85	11,817	1.88	1.28	9,255
Platinum + 5-FU	19,652	0.96	0.68	44,762	2.10	1.44	31,070
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

MSD would like to highlight that even with the further subgroup analyses, results come to the same conclusion as the overall population; which is, pembrolizumab in both the monotherapy and combination therapy regimens are cost-effective treatments compared to both EXTREME and platinum+5-FU.

A fully incremental analyses was not conducted by MSD. The NICE guide to the methods of technology appraisal states that “the Committee will normally be guided by established practice in the NHS when identifying appropriate comparator(s)”. It goes on to say, “the Committee’s overall decision on whether it is a valid comparator will be guided by whether it is recommended in extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology” (4). Based on these recommendations, MSD do not believe that a full incremental analysis is appropriate as neither pembrolizumab in the monotherapy nor combination therapy regimens is established practice or recommended by NICE, as stated in the NICE methods guide.

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6	The rationale given at the end of section 1 of the Appraisal Consultation Document for why the committee made their recommendations, which determined the nature of the requests for further clarification and analyses from the company listed in section 1.2, is based on the committee's assertion as stated in section 3.6 of the Appraisal Consultation Document that: "because current treatment options are different for cancer that started inside or outside the oral cavity in the NHS in England (see section 3.3), it was appropriate to consider the clinical effectiveness of pembrolizumab in the 2 population subgroups: cancer starting inside or outside the oral cavity". However, this reasoning is based on the assumption that the clinical effectiveness of pembrolizumab (both as monotherapy and in combination with platinum-based chemotherapy plus 5-fluorouracil) or its relevant comparators (cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil or just platinum-based chemotherapy plus 5-fluorouracil) differ depending on the site of tumour origin (specifically, in the oral cavity versus outside of the oral cavity), which is an assumption that is not supported by evidence. While the site of tumour origin is a determinant of which treatment a patient receives in the NHS in England, this is an artificial determinant not based on scientific clinical rationale (as pointed out during technical engagement, documented on pages 681-682 of the Committee papers PDF file). In short, this assumption/determinant is based solely on a set of underpowered statistically invalid subgroup analyses presented as part of the NICE technology appraisal of cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (TA172/TA473) where a set of 40 independent subgroup analyses testing at the 5% significance level were presented (shown in section 6.4 pages 46-48 of Merck Serono's submission for TA172), that did not actually include patients whose tumour originated outside of the oral cavity as a distinct subgroup for analysis. To contextualise how statistically invalid the results of these analyses are, a major publication on the topic of reporting of subgroup analyses in clinical trials (https://doi.org/10.1056/NEJMsr077003) points out that: "When multiple subgroup analyses are performed, the probability of a false positive finding can be substantial. For example, if the null hypothesis is true for each of 10 independent tests for interaction at the 0.05 significance level, the chance of at least one false positive result exceeds 40%" Accordingly, when 40 independent subgroup analyses testing at the 5% significance level are carried out, the chance of misleading false positive results would be considerably greater than 40% such that any of the individual results in this set of analyses loses scientifically rigorous informative value. The compromised nature of the validity of these subgroup analyses and consequently their unsuitability for use in decision-making was specifically pointed out in the publication for the pivotal trial that formed the foundation of the TA172/TA473 evidence base (https://doi.org/10.1056/NEJMoa0802656), which stated that: "There was a significant interaction with the primary tumor site, but because of repeated testing, this result could be due to chance. Such subgroup analyses must be interpreted cautiously; the results do not allow us to state with certainty that some groups did not benefit or to speculate on the degree of benefit." Furthermore, NICE's own guide to the methods of technology appraisal state that, with regard to the analysis of data for patient subgroups (section 5.10): Section 5.10.2: There should be a clear justification and, if appropriate, biological plausibility for the definition of the patient subgroup and the expectation of a differential effect. Post hoc data 'dredging' in search of subgroup effects is to be avoided and will be viewed sceptically. Section 5.10.7: The evidence supporting biological or clinical plausibility for a subgroup effect

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	should be fully documented, including details of statistical analysis. Therefore, in the absence of biological or clinical plausibility for a subgroup effect based on site of tumour origin for either pembrolizumab or the comparator (it is specifically noted in section 4.3 of the TA172 final appraisal determination document that "the specialists were not aware of any biological reason for cetuximab to be more clinically effective in oral cavity tumours"), the set of 40 analyses in search of subgroup effects used by the committee to justify the rationale for its recommendation, and the post hoc subgroup analyses requested now by the committee as part of this Appraisal Consultation Document, contradict these guidance. In addition, section 5.10.11 of the methods guide also states that: Types of subgroups that are not considered relevant are those based solely on the following factors: subgroups based solely on differential treatment costs for individuals according to their social characteristics As evidence for differences in the treatment effect of interventions in patients whose tumour originated in the oral cavity versus in patients whose tumour originated outside of the oral cavity is lacking, while there is evidence that shows there are distinct differences in the social characteristics between these patient groups (https://doi.org/10.1002/ijc.31416), and there are differential treatment costs between these patient groups in the NHS in England (as cetuximab in addition to platinum-based chemotherapy and 5-fluorouracil is currently only recommended by NICE for the treatment of the subgroup of patients whose cancer originated in the oral cavity), it is clear that the recommendations and requests from the committee in this Appraisal Consultation Document also contradict this section of guidance. Therefore, it is not appropriate for the committee to make their recommendation in this appraisal based on an underlying assumption that is flawed/unsupported by evidence to this degree, in a way that contradicts NICE's own published guidance on the processes and methods for technology appraisal.
7	With regard to the following statements in section 3.7 of the ACD: "The ERG explained that it was concerned about the analysis's validity because the company did not consider the plausibility of the hazard ratios estimated by the fractional polynomial model. The company did not say how the 2 categories of fractional polynomial models were assessed." This is not correct as MSD provided descriptions both of how the plausibility of the hazard ratios estimated by the fractional polynomial model were considered and how the 2 categories of fractional polynomial models were assessed as part of the technical engagement response form, as documented on page 12 of 38 of the technical engagement response from Merck Sharp & Dohme, shown on page 687 of 816 of the Committee papers PDF file.
8	With regard to the following statement in section 3.7 of the ACD: "The committee noted the results from the 2 approaches and considered that the company's approach may overestimate the effectiveness of pembrolizumab (monotherapy and in combination)" It should be noted that that MSD's approach that uses the fractional polynomial network meta-analysis is in fact more likely to *underestimate* the true effectiveness of pembrolizumab (monotherapy and in combination) versus platinum chemotherapy and 5-FU, as was explained on page 12 of 38 of the technical engagement response from Merck Sharp & Dohme, shown on page 687 of 816 of the Committee papers PDF file.

Insert extra rows as needed

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- 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.

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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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Appendix 1: Full comparison of baseline patient characteristics for the 2 subgroups: people whose cancer started inside or outside the oral cavity

A1.1: Patients in the KEYNOTE-048 study with PD-L1 CPS≥1 whose cancer originated in the oral cavity

Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Table 1 KEYNOTE-048 study patient characteristics, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	[redacted]					
Gender						
Male	[redacted]					
Female	[redacted]					
Age (Years)						
<65	[redacted]					
>=65	[redacted]					

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Mean	[redacted]					
SD						
Median						
Range						
Race						
American Indian Or Alaska Native						
Asian						
Black Or African American						
Multi-Racial						
White						
Ethnicity						
Hispanic Or Latino						
Not Hispanic Or Latino						
Not Reported						
Unknown						

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
	[redacted]		[redacted]		[redacted]	
Region Group						
NA	[redacted]		[redacted]		[redacted]	
EU	[redacted]		[redacted]		[redacted]	
ROW	[redacted]		[redacted]		[redacted]	
Smoking Status						
Never Smoker	[redacted]		[redacted]		[redacted]	
Ex Smoker	[redacted]		[redacted]		[redacted]	
Current Smoker	[redacted]		[redacted]		[redacted]	
Missing	[redacted]		[redacted]		[redacted]	
ECOG						
0	[redacted]		[redacted]		[redacted]	
1	[redacted]		[redacted]		[redacted]	
HPV Status						
Positive	[redacted]		[redacted]		[redacted]	
Negative	[redacted]		[redacted]		[redacted]	
PD-L1 TPS Status						
Strongly Positive	[redacted]		[redacted]		[redacted]	

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Not Strongly Positive	[redacted]					
PD-L1 CPS Status (CPS>=1)						
CPS >=1	[redacted]					
PD-L1 CPS Status (CPS>=20)						
CPS >=20	[redacted]					
CPS <20	[redacted]					
Missing	[redacted]					
PD-L1 CPS Status						
1<=CPS<20	[redacted]					
CPS>=20	[redacted]					
Baseline Tumor Size (mm) (Grouping by ITT Median)						
>=Median	[redacted]					
<Median	[redacted]					
Missing	[redacted]					

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects with data	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Median	[redacted]					
Range	[redacted]					
Disease Status						
Metastatic	[redacted]					
Recurrent	[redacted]					
Neither	[redacted]					
Primary Tumor Staging						
T0	[redacted]					
T1	[redacted]					
T2	[redacted]					
T3	[redacted]					
T4	[redacted]					

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
T4A	[redacted]					
T4B	[redacted]					
TX	[redacted]					
Regional Lymph Nodes Staging						
N0	[redacted]					
N1	[redacted]					
N2	[redacted]					
N3	[redacted]					
NX	[redacted]					
Metastatic Staging						
M0	[redacted]					
M1	[redacted]					
Overall Cancer Staging						
II	[redacted]					
III	[redacted]					

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
IVA	[redacted]					
IVB						
IVC						
Primary Tumor Location-Oral Cavity						
Yes						
Primary Tumor Location-Larynx						
Yes						
No						
Primary Tumor Location-Hypopharynx						
No						
Primary Tumor Location-Oropharynx						
Yes						
No						
Time from Latest Platinum Therapy (days)						
Subjects with data						
Mean						
SD						

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Median	[redacted]					
Range						
Time from Prior Systemic Therapy (days)						
Subjects with data						
Mean						
SD						
Median						
Range						
Database Cutoff Date: 25FEB2019						

Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Table 2 KEYNOTE-048 study patient characteristics, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
	[redacted]		[redacted]		[redacted]	
Gender						
Male	[redacted]		[redacted]		[redacted]	
Female	[redacted]		[redacted]		[redacted]	
Age (Years)						
<65	[redacted]		[redacted]		[redacted]	
>=65	[redacted]		[redacted]		[redacted]	
	[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	
Race						
American Indian Or Alaska Native	[redacted]		[redacted]		[redacted]	
Asian	[redacted]		[redacted]		[redacted]	
Black Or African American	[redacted]		[redacted]		[redacted]	

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Multi-Racial	[redacted]					
White	[redacted]					
Ethnicity						
Hispanic Or Latino	[redacted]					
Not Hispanic Or Latino	[redacted]					
Not Reported	[redacted]					
Unknown	[redacted]					
Region Group						
NA	[redacted]					
EU	[redacted]					
ROW	[redacted]					
Smoking Status						
Never Smoker	[redacted]					
Ex Smoker	[redacted]					
Current Smoker	[redacted]					
Missing	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
	[redacted]					
ECOG						
0	[redacted]					
1	[redacted]					
HPV Status						
Negative	[redacted]					
PD-L1 TPS Status						
Strongly Positive	[redacted]					
Not Strongly Positive	[redacted]					
PD-L1 CPS Status (CPS>=1)						
CPS >=1	[redacted]					
PD-L1 CPS Status (CPS>=20)						
CPS >=20	[redacted]					
CPS <20	[redacted]					
Missing	[redacted]					
PD-L1 CPS Status						
1<=CPS<20	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
CPS>=20	[redacted]					
Baseline Tumor Size (mm) (Grouping by ITT Median)						
>=Median	[redacted]					
<Median	[redacted]					
Missing	[redacted]					
Subjects with data	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Median	[redacted]					
Range	[redacted]					
Disease Status						
Metastatic	[redacted]					
Recurrent	[redacted]					
Neither	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
	[redacted]		[redacted]		[redacted]	
Primary Tumor Staging						
T0	[redacted]		[redacted]		[redacted]	
T1	[redacted]		[redacted]		[redacted]	
T2	[redacted]		[redacted]		[redacted]	
T3	[redacted]		[redacted]		[redacted]	
T4	[redacted]		[redacted]		[redacted]	
T4A	[redacted]		[redacted]		[redacted]	
T4B	[redacted]		[redacted]		[redacted]	
TX	[redacted]		[redacted]		[redacted]	
Regional Lymph Nodes Staging						
N0	[redacted]		[redacted]		[redacted]	
N1	[redacted]		[redacted]		[redacted]	
N2	[redacted]		[redacted]		[redacted]	
N3	[redacted]		[redacted]		[redacted]	
NX	[redacted]		[redacted]		[redacted]	

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
	[redacted]					
Metastatic Staging						
M0	[redacted]					
M1	[redacted]					
Overall Cancer Staging						
III	[redacted]					
IVA	[redacted]					
IVB	[redacted]					
IVC	[redacted]					
Primary Tumor Location-Oral Cavity						
Yes	[redacted]					
Primary Tumor Location-Larynx						
Yes	[redacted]					
No	[redacted]					
Primary Tumor Location-Hypopharynx						
No	[redacted]					
Primary Tumor Location-Oropharynx						
Yes	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
No	[redacted]					
Time from Latest Platinum Therapy (days)						
Subjects with data	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Median	[redacted]					
Range	[redacted]					
Time from Prior Systemic Therapy (days)						
Subjects with data	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Median	[redacted]					
Range	[redacted]					
Database Cutoff Date: 25FEB2019						

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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A1.2: Patients in the KEYNOTE-048 study with PD-L1 CPS≥1 whose cancer originated outside of the oral cavity

Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Table 3 KEYNOTE-048 study patient characteristics, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	[redacted]					
Gender						
Male	[redacted]					
Female	[redacted]					
Age (Years)						
<65	[redacted]					
>=65	[redacted]					
Mean	[redacted]					
SD	[redacted]					

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Median	[redacted]					
Range	[redacted]					
Race						
American Indian Or Alaska Native	[redacted]					
Asian	[redacted]					
Black Or African American	[redacted]					
Multi-Racial	[redacted]					
White	[redacted]					
Missing	[redacted]					
Ethnicity						
Hispanic Or Latino	[redacted]					
Not Hispanic Or Latino	[redacted]					
Not Reported	[redacted]					
Unknown	[redacted]					
Race Group						

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
White	[redacted]					
All Others	[redacted]					
Missing	[redacted]					
Region Group						
NA	[redacted]					
EU	[redacted]					
ROW	[redacted]					
Smoking Status						
Never Smoker	[redacted]					
Ex Smoker	[redacted]					
Current Smoker	[redacted]					
ECOG						
0	[redacted]					
1	[redacted]					
HPV Status						
Positive	[redacted]					

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Negative	[redacted]					
PD-L1 TPS Status						
Strongly Positive	[redacted]					
Not Strongly Positive	[redacted]					
PD-L1 CPS Status (CPS>=20)						
CPS >=20	[redacted]					
CPS <20	[redacted]					
Missing	[redacted]					
Baseline Tumor Size (mm) (Grouping by ITT Median)						
>=Median	[redacted]					
<Median	[redacted]					
Missing	[redacted]					
Subjects with data	[redacted]					
Mean	[redacted]					
SD	[redacted]					

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Median	[redacted]					
Range	[redacted]					
Disease Status						
Metastatic	[redacted]					
Recurrent	[redacted]					
Neither	[redacted]					
Brain Metastasis						
Yes	[redacted]					
No	[redacted]					
Metastatic Staging						
M0	[redacted]					
M1	[redacted]					
Overall Cancer Staging						
III	[redacted]					
IVA	[redacted]					
IVB	[redacted]					

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
IVC	[redacted]					
Primary Tumor Location-Oral Cavity						
No	[redacted]					
Primary Tumor Location-Larynx						
Yes	[redacted]					
No	[redacted]					
Primary Tumor Location-Hypopharynx						
Yes	[redacted]					
No	[redacted]					
Primary Tumor Location-Oropharynx						
Yes	[redacted]					
No	[redacted]					
Time from Latest Platinum Therapy (days)						
Subjects with data	[redacted]					
Mean	[redacted]					

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	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
SD	[redacted]					
Median						
Range						
Time from Prior Systemic Therapy (days)						
Subjects with data						
Mean						
SD						
Median						
Range						
Database Cutoff Date: 25FEB2019						

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Table 4 KEYNOTE-048 study patient characteristics, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	[redacted]					
Gender						
Male	[redacted]					
Female	[redacted]					
Age (Years)						
<65	[redacted]					
>=65	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Median	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Range	[redacted]					
Race						
American Indian Or Alaska Native	[redacted]					
Asian	[redacted]					
Black Or African American	[redacted]					
Multi-Racial	[redacted]					
White	[redacted]					
Missing	[redacted]					
Ethnicity						
Hispanic Or Latino	[redacted]					
Not Hispanic Or Latino	[redacted]					
Not Reported	[redacted]					
Unknown	[redacted]					
Race Group						
White	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
All Others	[redacted]					
Missing	[redacted]					
Region Group						
NA	[redacted]					
EU	[redacted]					
ROW	[redacted]					
Smoking Status						
Never Smoker	[redacted]					
Ex Smoker	[redacted]					
Current Smoker	[redacted]					
ECOG						
0	[redacted]					
1	[redacted]					
HPV Status						
Positive	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Negative	[redacted]					
PD-L1 TPS Status						
Strongly Positive	[redacted]					
Not Strongly Positive	[redacted]					
PD-L1 CPS Status (CPS>=20)						
CPS >=20	[redacted]					
CPS <20	[redacted]					
Missing	[redacted]					
Baseline Tumor Size (mm) (Grouping by ITT Median)						
>=Median	[redacted]					
<Median	[redacted]					
Missing	[redacted]					
Subjects with data	[redacted]					
Mean	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
SD	[redacted]					
Median	[redacted]					
Range	[redacted]					
Disease Status						
Metastatic	[redacted]					
Recurrent	[redacted]					
Neither	[redacted]					
Brain Metastasis						
Yes	[redacted]					
No	[redacted]					
Metastatic Staging						
M0	[redacted]					
M1	[redacted]					
Overall Cancer Staging						
III	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
IVA	[redacted]					
IVB	[redacted]					
IVC	[redacted]					
Primary Tumor Location-Oral Cavity						
No	[redacted]					
Primary Tumor Location-Larynx						
Yes	[redacted]					
No	[redacted]					
Primary Tumor Location-Hypopharynx						
Yes	[redacted]					
No	[redacted]					
Primary Tumor Location-Oropharynx						
Yes	[redacted]					
No	[redacted]					
Time from Latest Platinum Therapy (days)						
Subjects with data	[redacted]					

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Mean	[redacted]					
SD						
Median						
Range						
Time from Prior Systemic Therapy (days)						
Subjects with data						
Mean						
SD						
Median						
Range						

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	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Database Cutoff Date: 25FEB2019						

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Appendix 2: Subgroup analyses of overall survival according to relevant prognostic factors

A2.1: Patients in the KEYNOTE-048 study with PD-L1 CPS≥1 whose cancer originated in the oral cavity

Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Figure 1 Forest plot of OS hazard ratio by subgroup factors, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Figure 2 Forest plot of OS hazard ratio by subgroup factors, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

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A3.2: Patients in the KEYNOTE-048 study with PD-L1 CPS≥1 whose cancer originated outside of the oral cavity

Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Figure 3 Forest plot of OS hazard ratio by subgroup factors, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

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Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Figure 4 Forest plot of OS hazard ratio by subgroup factors, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Appendix 3: Overall survival data for the 2 subgroups: people whose cancer started inside or outside the oral cavity

A3.1: Patients in the KEYNOTE-048 study with PD-L1 CPS≥1 whose cancer originated in the oral cavity

Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Overall survival – results not adjusted for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor

Table 5 Analysis of overall survival, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Primary Pembrolizumab vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
§ One-sided p-value based on log-rank test.
Database Cutoff Date: 25FEB2019

Table 6 Overall survival rate, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

	Pembrolizumab [redacted]	Cetuximab + Chemotherapy [redacted]
OS rate at 6 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 12 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 18 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 24 Months in (95% CI)†	[redacted]	[redacted]

† From the product-limit (Kaplan-Meier) method for censored data.
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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Figure 5 Kaplan-Meier estimates of overall survival, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

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Overall survival – adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Patient disposition for Stage 1

Figure 6 Disposition of the control group with regard to switch-over, ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab monotherapy versus cetuximab + chemotherapy)

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Figure 7 Kaplan-Meier curves of time to switch-over from disease progression switching patients from control arm eligible for switch-over to immune checkpoint inhibitors, ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab monotherapy versus cetuximab + chemotherapy)

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Table 7 Patient characteristics patients from standard treatment arm eligible to receive subsequent immune checkpoint inhibitors, comparison of switchers vs. non-switchers (Stage 1 model), ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab monotherapy vs. cetuximab + chemotherapy)

	Study: 3475-048

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Characteristic	Switchers [redacted]	Non-Switchers [redacted]	p-value ‡ Switchers vs Non-Switchers
CPS Category at Baseline			
CPS ≥20%	[redacted]	[redacted]	[redacted]
CPS <20%	[redacted]	[redacted]	[redacted]
HPV Status			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Chemotherapy			
Cisplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
ECOG status at Secondary Baseline §			
0	[redacted]	[redacted]	[redacted]
≥1	[redacted]	[redacted]	[redacted]
Race			
White	[redacted]	[redacted]	[redacted]
All Others	[redacted]	[redacted]	[redacted]
Hemoglobin(gm/l) at Secondary Baseline §			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]
Tumor Size at Secondary Baseline §			
Subjects with data	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]

† Patients were eligible to switch if they had documented progression.

‡ Two-sided p-values based on Chi-square test for categorical variables and t-test for continuous variables

§ Secondary baseline defined as time of disease progression.

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Table 8 Parameter estimates - Stage 1 model (lognormal distribution)‡, patients from control arm eligible for switch-over to immune checkpoint inhibitors§, ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1 (from comparison of pembrolizumab monotherapy vs. cetuximab + chemotherapy)

Parameter	Estimate	Standard Error	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Switching Factor (Switchers vs. Non-switchers)	[redacted]	[redacted]	[redacted]	[redacted]
CPS Category at Baseline (<20% vs. >=20%)	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy (Cisplatin vs. Carboplatin)	[redacted]	[redacted]	[redacted]	[redacted]
Race (All Others vs. White)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Hemoglobin at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Tumor Size at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Convergence Statistics			[redacted]	[redacted]

‡ Lognormal survival model for the standard treatment group using secondary baseline in time-to-event calculations, and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (All others vs. White), hemoglobin at secondary baseline and tumor size at secondary baseline.

§ Patients were eligible to switch if they had documented progression.

† Secondary baseline defined as time of disease progression.

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Estimation of treatment effect (Stage 2, results)

Table 9 Analysis of overall survival, adjusting for patients in the cetuximab in combination with platinum and 5-FU chemotherapy arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

				Event Rate/	Median OS†	OS Rate at	Treatment vs. Cetuximab + Chemotherapy

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Treatment	N	Number of Events (%)	Person-Months	100 Person-Months (%)	(Months) (95% CI)	Month 12 in %[†] (95% CI)	Hazard Ratio[‡] (95% CI)[‡]	p-Value[¶¶]	p-Value[‖]
Cetuximab + Chemotherapy	[redacted]								
Cetuximab + Chemotherapy, 2-stage adjusted[¶]	[redacted]								
Pembrolizumab	[redacted]								

Stage 1 model[††]	Acceleration factor[‡‡]
[§] Controls eligible to cross-over to immune checkpoint inhibitors, patients switching vs patients not switching	[redacted]

[¶] Survival times shrunk for the patients who actually crossed-over to immune checkpoint inhibitors.

[†] From product-limit (Kaplan-Meier) method for censored data.

[‡] Based on Cox regression model with Efron′s method of tie handling with treatment as a covariate. The 95% CI is derived by adjusting the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[¶¶] Two sided p-value based on Cox model, ITT population, analysis not adjusted for treatment switch.

[‖] Two sided p-value based on log-rank test, ITT population, analysis not adjusted for treatment switch.

[††] Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (White vs. All others), hemoglobin at secondary baseline and tumor size at secondary baseline.

[§] Patients were eligible to switch if they had documented progression.

[‡‡] Acceleration factor used to shrink the survival time of standard treatment patients who actually received subsequent immune checkpoint inhibitors. Its estimate and the 95% CI are derived from Stage 1 Lognormal model.

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Figure 8 Kaplan-Meier estimates of overall survival, adjusting for patients in the cetuximab in combination with platinum and 5-FU chemotherapy arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Overall survival – results not adjusted for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor

Table 10 Analysis of overall survival, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Primary Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
† From product-limit (Kaplan-Meier) method for censored data.						
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.						
§ One-sided p-value based on log-rank test.						
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Table 11 Overall survival rate, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

	Pembrolizumab + Chemotherapy [redacted]	Cetuximab + Chemotherapy [redacted]
OS rate at 6 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 12 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 18 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 24 Months in (95% CI)†	[redacted]	[redacted]
† From the product-limit (Kaplan-Meier) method for censored data.		
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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Figure 9 Kaplan-Meier estimates of overall survival, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

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Overall survival – adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

Patient disposition for Stage 1

Figure 10 Disposition of the control group with regard to switch-over, ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy)

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Figure 11 Kaplan-Meier curves of time to switch-over from disease progression switching patients from control arm eligible for switch-over to immune checkpoint inhibitors, ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy)

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Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140]

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Table 12 Patient characteristics patients from standard treatment arm eligible to receive subsequent immune checkpoint inhibitors, comparison of switchers vs. non-switchers (Stage 1 model), ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy)

Characteristic	Study: 3475-048		
	Switchers [redacted]	Non-Switchers [redacted]	p-value ‡ Switchers vs Non-Switchers
CPS Category at Baseline			
CPS ≥20%	[redacted]	[redacted]	[redacted]
CPS <20%	[redacted]	[redacted]	[redacted]
HPV Status			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Chemotherapy			
Cisplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
ECOG status at Secondary Baseline §			
0	[redacted]	[redacted]	[redacted]
≥1	[redacted]	[redacted]	[redacted]
Race			
White	[redacted]	[redacted]	[redacted]
All Others	[redacted]	[redacted]	[redacted]
Hemoglobin(gm/l) at Secondary Baseline §			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]
Tumor Size at Secondary Baseline §			
Subjects with data	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

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Characteristic	Study: 3475-048		
	Switchers [redacted]	Non-Switchers [redacted]	p-value ‡ Switchers vs Non-Switchers
Median (Range)	[redacted]	[redacted]	[redacted]

† Patients were eligible to switch if they had documented progression.

‡ Two-sided p-values based on Chi-square test for categorical variables and t-test for continuous variables

§ Secondary baseline defined as time of disease progression.

Database Cutoff Date: 25FEB2019.

Table 13 Parameter estimates - Stage 1 model (lognormal distribution)‡, patients from control arm eligible for switch-over to immune checkpoint inhibitors§, ITT population, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1 (from comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy)

Parameter	Estimate	Standard Error	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Switching Factor (Switchers vs. Non-switchers)	[redacted]	[redacted]	[redacted]	[redacted]
CPS Category at Baseline (<20% vs. >=20%)	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy (Cisplatin vs. Carboplatin)	[redacted]	[redacted]	[redacted]	[redacted]
Race (All Others vs. White)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Hemoglobin at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Tumor Size at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Convergence Statistics			AIC	[redacted]

‡ Lognormal survival model for the standard treatment group using secondary baseline in time-to-event calculations, and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (All others vs. White), hemoglobin at secondary baseline and tumor size at secondary baseline.

§ Patients were eligible to switch if they had documented progression.

† Secondary baseline defined as time of disease progression.

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Estimation of treatment effect (Stage 2, results)

Table 14 Analysis of overall survival, adjusting for patients in the cetuximab in combination with platinum and 5-FU chemotherapy arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio‡ (95% CI)‡	p-Value¶	p-Value‖
Cetuximab + Chemotherapy	[redacted]								
Cetuximab + Chemotherapy, 2-stage adjusted¶	[redacted]								
Pembrolizumab + Chemotherapy	[redacted]								
Stage 1 model††							Acceleration factor‡‡		
§ Controls eligible to cross-over to immune checkpoint inhibitors, patients switching vs patients not switching							[redacted]		

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Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in %[†] (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[¶¶]	p-Value[‖]

[¶] Survival times shrunk for the patients who actually crossed-over to immune checkpoint inhibitors.

[†] From product-limit (Kaplan-Meier) method for censored data.

[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate. The 95% CI is derived by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[¶¶] Two sided p-value based on Cox model, ITT population, analysis not adjusted for treatment switch.

[‖] Two sided p-value based on log-rank test, ITT population, analysis not adjusted for treatment switch.

[††] Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (White vs. All others), hemoglobin at secondary baseline and tumor size at secondary baseline.

[§] Patients were eligible to switch if they had documented progression.

[‡‡] Acceleration factor used to shrink the survival time of standard treatment patients who actually received subsequent immune checkpoint inhibitors. Its estimate and the 95% CI are derived from Stage 1 Lognormal model.

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Figure 12 Kaplan-Meier estimates of overall survival, adjusting for patients in the cetuximab in combination with platinum and 5-FU chemotherapy arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated in the oral cavity and with PD-L1 CPS≥1

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A3.2: Patients in the KEYNOTE-048 study with PD-L1 CPS≥1 whose cancer originated outside of the oral cavity

Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Overall survival – results not adjusted for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor

Table 15 Analysis of overall survival, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Primary Pembrolizumab vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

§ One-sided p-value based on log-rank test.

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Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
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Table 16 Overall survival rate, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

	Pembrolizumab [redacted]	Cetuximab + Chemotherapy [redacted]
OS rate at 6 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 12 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 18 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 24 Months in (95% CI)†	[redacted]	[redacted]
† From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 25FEB2019		

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Figure 13 Kaplan-Meier estimates of overall survival, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

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Overall survival – adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

Patient disposition for Stage 1

Figure 14 Disposition of the control group with regard to switch-over, ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab monotherapy versus cetuximab + chemotherapy)

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Figure 15 Kaplan-Meier curves of time to switch-over from disease progression switching patients from control arm eligible for switch-over to immune checkpoint inhibitors, ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab monotherapy versus cetuximab + chemotherapy)

Table 17 Patient characteristics patients from standard treatment arm eligible to receive subsequent immune checkpoint inhibitors, comparison of switchers vs. non-switchers (Stage 1 model), ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab monotherapy vs. cetuximab + chemotherapy)

	Study: 3475-048		
Characteristic	Switchers	Non-Switchers	p-value ‡

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	[redacted]	[redacted]	Switchers vs Non-Switchers
CPS Category at Baseline			
CPS ≥20%	[redacted]	[redacted]	[redacted]
CPS <20%	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
HPV Status			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Chemotherapy			
Cisplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
ECOG status at Secondary Baseline §			
0	[redacted]	[redacted]	[redacted]
≥1	[redacted]	[redacted]	[redacted]
Race			
White	[redacted]	[redacted]	[redacted]
All Others	[redacted]	[redacted]	[redacted]
Hemoglobin(gm/l) at Secondary Baseline §			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]
Tumor Size at Secondary Baseline §			
Subjects with data	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]

† Patients were eligible to switch if they had documented progression.

‡ Two-sided p-values based on Chi-square test for categorical variables and t-test for continuous variables

§ Secondary baseline defined as time of disease progression.

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Table 18 Parameter estimates - Stage 1 model (lognormal distribution)‡, patients from control arm eligible for switch-over to immune checkpoint inhibitors§, ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1 (from comparison of pembrolizumab monotherapy vs. cetuximab + chemotherapy)

Parameter	Estimate	Standard Error	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Switching Factor (Switchers vs. Non-switchers)	[redacted]	[redacted]	[redacted]	[redacted]
CPS Category at Baseline (<20% vs. >=20%)	[redacted]	[redacted]	[redacted]	[redacted]
HPV Status (Positive vs. Negative)	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy (Cisplatin vs. Carboplatin)	[redacted]	[redacted]	[redacted]	[redacted]
Race (All Others vs. White)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Hemoglobin at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Tumor Size at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Convergence Statistics			AIC	[redacted]

‡ Lognormal survival model for the standard treatment group using secondary baseline in time-to-event calculations, and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (All others vs. White), hemoglobin at secondary baseline and tumor size at secondary baseline.

§ Patients were eligible to switch if they had documented progression.

† Secondary baseline defined as time of disease progression.

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Estimation of treatment effect (Stage 2, results)

Table 19 Analysis of overall survival, adjusting for patients in the cetuximab in combination with platinum and 5-FU chemotherapy arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio‡ (95% CI)‡	p-Value¶	p-Value‖
Cetuximab + Chemotherapy	[redacted]								
Cetuximab + Chemotherapy, 2-stage adjusted¶	[redacted]								
Pembrolizumab	[redacted]								
Stage 1 model††							Acceleration factor‡‡		
§ Controls eligible to cross-over to immune checkpoint inhibitors, patients switching vs patients not switching							[redacted]		

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Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in %[†] (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[¶¶]	p-Value[‖]

[¶] Survival times shrunk for the patients who actually crossed-over to immune checkpoint inhibitors.

[†] From product-limit (Kaplan-Meier) method for censored data.

[‡] Based on Cox regression model with Efron′s method of tie handling with treatment as a covariate. The 95% CI is derived by adjusting the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[¶¶] Two sided p-value based on Cox model, ITT population, analysis not adjusted for treatment switch.

[‖] Two sided p-value based on log-rank test, ITT population, analysis not adjusted for treatment switch.

[††] Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (White vs. All others), hemoglobin at secondary baseline and tumor size at secondary baseline.

[§] Patients were eligible to switch if they had documented progression.

[‡‡] Acceleration factor used to shrink the survival time of standard treatment patients who actually received subsequent immune checkpoint inhibitors. Its estimate and the 95% CI are derived from Stage 1 Lognormal model.

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Figure 16 Kaplan-Meier estimates of overall survival, adjusting for patients in the cetuximab in combination with platinum and 5-FU chemotherapy arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population, pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

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[redacted]

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Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Overall survival – results not adjusted for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor

Table 20 Analysis of overall survival, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Primary Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

§ One-sided p-value based on log-rank test.

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Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Database Cutoff Date: 25FEB2019						

Table 21 Overall survival rate, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside the oral cavity and with PD-L1 CPS≥1

	Pembrolizumab + Chemotherapy (N=165)	Cetuximab + Chemotherapy (N=162)
OS rate at 6 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 12 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 18 Months in (95% CI)†	[redacted]	[redacted]
OS rate at 24 Months in (95% CI)†	[redacted]	[redacted]
† From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 25FEB2019		

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Figure 17 Kaplan-Meier estimates of overall survival, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

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Overall survival – adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

Patient disposition for Stage 1

Figure 18 Disposition of the control group with regard to switch-over, ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy)

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Figure 19 Kaplan-Meier curves of time to switch-over from disease progression switching patients from control arm eligible for switch-over to immune checkpoint inhibitors, ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy)

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Table 22 Patient characteristics patients from standard treatment arm eligible to receive subsequent immune checkpoint inhibitors, comparison of switchers vs. non-switchers (Stage 1 model), ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1 (from the comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy)

Characteristic	Study: 3475-048		
	Switchers N=31	Non-Switchers N=70	p-value ‡ Switchers vs Non-Switchers
CPS Category at Baseline			
CPS ≥20%	[redacted]	[redacted]	[redacted]
CPS <20%	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
HPV Status			
Positive	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]
Chemotherapy			
Cisplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
ECOG status at Secondary Baseline §			
0	[redacted]	[redacted]	[redacted]
≥1	[redacted]	[redacted]	[redacted]
Race			
White	[redacted]	[redacted]	[redacted]
All Others	[redacted]	[redacted]	[redacted]
Hemoglobin(gm/l) at Secondary Baseline §			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]
Tumor Size at Secondary Baseline §			
Subjects with data	[redacted]	[redacted]	[redacted]

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Characteristic	Study: 3475-048		
	Switchers N=31	Non-Switchers N=70	p-value ‡ Switchers vs Non-Switchers
Mean (SD) Median (Range)	[redacted]	[redacted]	[redacted]

† Patients were eligible to switch if they had documented progression.

‡ Two-sided p-values based on Chi-square test for categorical variables and t-test for continuous variables

§ Secondary baseline defined as time of disease progression.

Database Cutoff Date: 25FEB2019.

Table 23 Parameter estimates - Stage 1 model (lognormal distribution)‡, patients from control arm eligible for switch-over to immune checkpoint inhibitors§, ITT population, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1 (from comparison of pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy)

Parameter	Estimate	Standard Error	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Switching Factor (Switchers vs. Non-switchers)	[redacted]	[redacted]	[redacted]	[redacted]
CPS Category at Baseline (<20% vs. >=20%)	[redacted]	[redacted]	[redacted]	[redacted]
HPV Status (Positive vs. Negative)	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy (Cisplatin vs. Carboplatin)	[redacted]	[redacted]	[redacted]	[redacted]
Race (All Others vs. White)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Hemoglobin at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Tumor Size at Secondary Baseline †	[redacted]	[redacted]	[redacted]	[redacted]
Convergence Statistics			AIC	[redacted]

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Parameter	Estimate	Standard Error	95% CI	p-value
‡ Lognormal survival model for the standard treatment group using secondary baseline in time-to-event calculations, and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (All others vs. White), hemoglobin at secondary baseline and tumor size at secondary baseline.				
§ Patients were eligible to switch if they had documented progression.				
† Secondary baseline defined as time of disease progression.				
Database Cutoff Date: 25FEB2019.				

Estimation of treatment effect (Stage 2, results)

Table 24 Analysis of overall survival, adjusting for patients in the cetuximab in combination with platinum and 5-FU chemotherapy arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio‡ (95% CI)‡	p-Value¶	p-Value‖
Cetuximab + Chemotherapy	[redacted]								
Cetuximab + Chemotherapy, 2-stage adjusted¶	[redacted]								
Pembrolizumab + Chemotherapy	[redacted]								
Stage 1 model††							Acceleration factor‡‡		
§ Controls eligible to cross-over to immune checkpoint inhibitors, patients switching vs patients not switching							[redacted]		

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Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in %[†] (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[¶¶]	p-Value[‖]

[¶] Survival times shrunk for the patients who actually crossed-over to immune checkpoint inhibitors.

[†] From product-limit (Kaplan-Meier) method for censored data.

[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate. The 95% CI is derived by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[¶¶] Two sided p-value based on Cox model, ITT population, analysis not adjusted for treatment switch.

[‖] Two sided p-value based on log-rank test, ITT population, analysis not adjusted for treatment switch.

[††] Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (White vs. All others), hemoglobin at secondary baseline and tumor size at secondary baseline.

[§] Patients were eligible to switch if they had documented progression.

[‡‡] Acceleration factor used to shrink the survival time of standard treatment patients who actually received subsequent immune checkpoint inhibitors. Its estimate and the 95% CI are derived from Stage 1 Lognormal model.

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Figure 20 Kaplan-Meier estimates of overall survival, adjusting for patients in the cetuximab in combination with platinum and 5-FU chemotherapy arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population, pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy, patients whose cancer originated outside of the oral cavity and with PD-L1 CPS≥1

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Appendix 4: OS Extrapolation Curves

A4.1: Oral Cavity Subgroup

Table 25: Monotherapy Goodness-of-fit

Fitted Function	Pembrolizumab Monotherapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	105.5	106.6	6	129.7	130.8	5
Weibull	104.4	106.6	5	124.9	126.9	3
Gompertz	101.1	103.3	1	126.8	128.9	4
Log-logistic	103.6	105.8	3	124.2	126.3	2
Log-normal	102.9	105.1	2	123.4	125.5	1
Generalised Gamma	103.8	107.1	4	0	0	6

Table 26: Combination Therapy Goodness-of-fit

Fitted Function	Pembrolizumab Combination therapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	96.1	97.2	1	126.7	130.8	5
Weibull	97.8	100	5	124.9	126.9	3
Gompertz	97.7	99.9	4	126.8	128.9	4
Log-logistic	97.7	99.8	3	124.2	126.3	2

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Fitted Function	Pembrolizumab Combination therapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Log-normal	97.1	99.3	2	123.4	125.5	1
Generalised Gamma	0	0	6	0	0	6

Table 27: 5-year Follow-up Data of the EXTREME Study at Random Time Points

Treatment arm	% of patients alive at 28 months (1376 days)	% of patients alive at 36 months (1769 days)	% of patients alive at 42 months (2064 days)	% of patients alive at 59.5 months (2924 days)
	Trial	Trial	Trial	Trial
Cetuximab	11.7	7.1	6.5	2.9
Standard of Care (platinum +5-FU)	8.3	4.4	4.4	1.7
Increment	3.4	2.7	2.1	1.2

Table 28: Summary of Survival Estimates Based on Curve Selection with 5-Year Treatment Waning (Pembrolizumab Monotherapy)

Years after Treatment	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma
1	35.9	35.9	35.9	35.9	35.9	35.9
2	22.6	20.8	19.2	20.4	20.4	19.7
5	5.9	10.3	15.8	10.9	11.4	13.2
10	0.2	4.1	14.7	6.8	7.0	0.1

Table 29: Summary of Survival Estimates Based on Curve Selection with 5-Year Treatment Waning (Pembrolizumab Combination Therapy)

Years after Treatment	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma
1	46.7	46.7	46.7	46.7	46.7	46.7
2	22.6	22.1	21.8	21.8	21.7	0
5	6.9	8.7	11.9	10.3	10.8	0
10	0.2	3.5	11.0	6.4	6.6	0

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Table 30: Summary of Survival Estimates Based on Curve Selection with 5-Year Treatment Waning (Cetuximab + Platinum + 5-FU)

Years after Treatment	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma
1	41.3	41.3	41.3	41.3	41.3	41.3
2	17.6	15.1	14.4	14.5	14.5	0
5	2.2	5.8	8.7	6.7	6.8	0
10	0.1	2.3	8.1	4.2	4.2	0

Table 31: Summary of Survival Estimates Based on Log-normal and Weibull Curve Selection with 5-Year Treatment Waning for pembrolizumab arms and Cetuximab + Platinum + 5-FU Respectively

Years after treatment	Pembrolizumab monotherapy	Pembrolizumab Combination Therapy	Cetuximab + platinum + 5-FU
1	35.9	46.7	41.3
2	20.4	21.7	15.1
5	11.3	10.8	5.8
10	4.5	4.3	2.3

A4.2: Non-oral Cavity Subgroup

Table 32:Monotherapy Goodness-of-fit

Fitted Function	Pembrolizumab Monotherapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	351.6	353.9	1	241.9	243.6	4
Weibull	352.8	357.4	2	243.7	247.0	6
Gompertz	353.1	357.8	3	243.0	246.3	5
Log-logistic	353.2	357.8	4	239.0	242.3	2
Log-normal	356.4	361.1	5	238.2	241.5	1
Generalised Gamma	0	0	6	238.6	243.5	3

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Table 33: Combination Therapy Goodness-of-fit

Fitted Function	Pembrolizumab Combination therapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	252.1	254.3	3	241.9	243.6	4
Weibull	251.8	256.3	6	243.7	247.0	6
Gompertz	250.2	254.8	2	243.0	246.3	5
Log-logistic	251.2	255.7	4	239.0	242.3	2
Log-normal	249.9	254.4	1	238.2	241.5	1
Generalised Gamma	250.6	257.3	5	238.6	243.5	3

Table 34: Summary of Survival Estimates Based on Curve Selection with 5-Year Treatment Waning (Pembrolizumab Monotherapy and Combination Therapy)

Years after Treatment	Exponential		Weibull		Gompertz		Log-logistic		Log-normal		Generalised gamma	
	Mono	Combo	Mono	Combo	Mono	Combo	Mono	Combo	Mono	Combo	Mono	Combo
1	55.8	57.5	55.8	57.5	55.8	57.5	55.8	57.5	55.8	57.5	55.8	57.5
2	34.2	37.8	33.3	36.5	33.4	35.7	33.1	36.2	32.3	36.0	0	35.1
5	9.7	16.5	11.8	20.5	13.8	27.0	14.6	21.9	17.0	22.9	0	26.1
10	0.1	0.1	0	0	9.0	17.6	3.8	5.7	2.5	3.4	0	11.1

Table 35: Summary of Survival Estimates Based on Curve Selection vs Monotherapy and Combination Therapy with 5-Year Treatment Waning (Platinum + 5-FU)

Years after Treatment	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma
1	42.0	42.0	42.0	42.0	42.0	42.0
2	14.4	14.7	13.6	14.0	14.2	13.5
5	0.8	0.5	3.0	1.5	1.5	2.8
10	0	0	1.9	0.4	0.2	1.2

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	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):	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
Name of commentator person completing form:	[redacted]

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.
1	Our experts are concerned that this recommendation is not a sound and suitable basis for guidance to the NHS due to the recommendation being based upon the premise that the use of cetuximab in non-oral cavity HNSCC does not reflect clinical practice in the NHS in England. The restriction on the use of cetuximab to the oral cavity subgroup was a health economic decision made by NICE based on a sub-group analysis of the original study of chemotherapy with or without cetuximab (Vermorken, NEJM, 2008). The rationale was that a sub-group analysis of the whole group treated with chemotherapy + cetuximab showed that the greatest survival gains were seen in oral cavity group -and the improvements in survival with cetuximab in the non-oral cavity group did not reach statistical significance. This restriction to the use of cetuximab to oral cavity has not been adopted internationally and as the study was required to have international recruitment, the restriction of cetuximab to the oral-cavity subgroup would have been considered unethical in all other health care systems outside the NHS in England as being inferior to the standard of care. As such, it was an appropriate comparator arm in the study design. Moreover, the data from this same sub-group analysis (Vermorken NEJM 2008) did not show any evidence that cetuximab use was associated with worse outcomes. As such, it is not plausible to assume that the inclusion of cetuximab in the comparator arm for patients with non-oral cavity disease would increase the apparent efficacy of the pembrolizumab treated patients in the experimental arms, it would be expected to show the converse.

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- 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.

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- 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.

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

A MEMBER OF THE RUSSELL GROUP

This report comprises the ERG's response to the company response to ACD1 as well as the ERG's responses to requests from NICE (issued in emails dated 28/02/20 and 0/03/2020) which arose following NICE's examination of the CRA1 document.

2 ERG RESPONSE

2.1 Imbalances in baseline characteristics

NICE request #1: *Provide full comparison of baseline patient characteristics for people whose cancer started inside the oral cavity and for people whose cancer started outside of the oral cavity (the oral and non-oral subgroups).*

NICE request #2: *Provide overall survival data for the two subgroups (Kaplan-Meier [K-M] data, hazard ratios) for the two subgroups. Carry out formal statistical analyses to adjust for imbalances in baseline patient characteristics in the subgroups. Justify which adjustment method was used and do not restrict it to just the co-variates that are unbalanced.*

The ERG highlights that analyses by primary tumour location (oral or non-oral) were not pre-specified in the KEYNOTE-048 trial statistical analysis plan. The CONSORT (Consolidated Standards of Reporting Trials) initiative is strongly critical of post-hoc analyses and questions their credibility at large.[1] Further, as the KEYNOTE-048 trial was not powered to show differences by these subgroups, results from these analyses can only be considered as hypothesis generating; they should not be considered as evidence.[2]

In the CRA1 document (comment #6) the company outlines their reasons as to why they do not consider it appropriate to consider effectiveness/cost effectiveness by origin of primary tumour. The ERG agrees with the company that the decision to treat patients in the NHS based on site of tumour origin is based solely on a set of underpowered statistically invalid subgroup analyses presented as part of the NICE technology appraisal of cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (TA172/TA473).

However, the company has provided a comparison of baseline characteristics in CRA1 comment #1 and provided their rationale for not making any adjustments in comment #2. In summary, using data from the KEYNOTE-048 trial, the company assessed imbalances in ten baseline characteristics (age, sex, race, European Co-operative Oncology Group (ECOG performance status [PS] score, region, smoking status, disease status PD-L1, CPS [combined positive score) and TPS [tumour proportion score], and baseline tumour size) for the following populations and treatments:

1. oral: pembrolizumab monotherapy (n=75) versus cetuximab+PLAT+5-FU (n=80)
2. oral: pembrolizumab+PLAT+5-FU (n=77) versus cetuximab+PLAT+5-FU (n=73)
3. non-oral: pembrolizumab monotherapy (n=182) versus cetuximab+PLAT+5-FU (n=175)
4. non-oral: pembrolizumab+PLAT+5-FU (n=165) versus cetuximab+PLAT+5-FU (n=162).

Detailed company results are provided in forest plots (Figures 1 to 4 of the CRA1 Appendix). These results show that the differences between subgroups/trial arms are not statistically significantly different for any of the baseline characteristics. The ERG, therefore, considers that no adjustments are required.

2.2 OS and PFS estimates for the oral and non-oral subgroups

NICE request #3: *Provide OS extrapolation curves, after adjusting for imbalances in baseline patient characteristics for the two subgroups, and justify the choice of distribution used.*

The ERG highlights that cetuximab+PLAT+5-FU has not been recommended by NICE for treating patients with non-oral cancer and clinical advice to the ERG is that it is not a treatment that is used in NHS clinical practice for this group of patients. Therefore, this comparison should be outside of the scope of this appraisal. The appropriate comparator for this subgroup is PLAT+5-FU. There is no direct evidence comparing pembrolizumab (monotherapy or in combination) versus PLAT+5-FU. However, the ERG considers that data from the EXTREME trial, a multi-centre, phase III trial of cetuximab+PLAT+5-FU versus PLAT+5-FU in patients with R/M HNSCC, show that data from the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial can be used as a proxy for the overall survival (OS) experience of non-oral cavity patients receiving PLAT+5-FU. This is because results from the EXTREME trial have shown that, for each of three distinct non-oral patient subgroups, there was no statistically significant evidence that treatment with cetuximab+PLAT+5-FU increased OS versus treatment with PLAT+5-FU.

The progression-survival (PFS) results from the EXTREME trial do show differences by origin of cancer. However, for the 'combined non-oral subgroup', the gain in median PFS from treatment with cetuximab+PLAT+5-FU versus PLAT+5-FU is unlikely to be more than 1.6 months. This difference should be taken into account if KEYNOTE-048 cetuximab+PLAT+5-FU PFS data are used to model the experience of non-oral cavity patients receiving PLAT+5-FU.

As explained in the original ERG report, overall survival (OS) and PFS Kaplan-Meier (K-M) data from the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial 'all-comers' population can be used to model the experience of patients in both the oral and non-oral cavity subgroups receiving cetuximab+PLAT+5-FU. The OS and PFS K-M data from KEYNOTE-048 trial

‘pembrolizumab monotherapy datasets’ are displayed in

Figure 1 and Figure 2 respectively. Similar figures have been generated for the ‘pembrolizumab+PLAT+5-FU datasets’ and can be found in Appendix A.1.

Figure 1 Keynote-048 trial Kaplan-Meier overall survival data for patients treated receiving cetuximab+PLAT+5-FU (versus pembrolizumab monotherapy)

Source: Company model submitted in response to the first ACD

Figure 2 Keynote-048 trial progression-free survival data for patients treated with cetuximab+PLAT+5-FU (versus pembrolizumab monotherapy)

Source: Company model submitted in response to the first ACD

Within an email (dated 28/02/2020), NICE sought the ERG's view on the effect of treatment switching. In the original CS, the company presented results from an analysis that adjusted for the fact that many patients in the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial (206 events) switched from the control treatment to an immune checkpoint inhibitors post-study treatment. The company used the 2-stage method to adjust for switching. The adjustment made by the company (to the cetuximab+PLAT+5-FU dataset used in the comparison with pembrolizumab monotherapy) had the effect of changing median OS from 10.3 months (95% confidence interval [CI]: 9.0 to 11.5 months) to 10.1 months (95% CI: 9.0 to 11.5 months). Further, data displayed in the original CS (Figure 6) showed that the effect of adjusting for treatment switching had on the trajectory of the OS K-M data for this data set was negligible. The company results after adjusting for treatment switching on the cetuximab+PLAT+5-FU dataset that was used for the comparison with pembrolizumab+PLAT+5-FU were of a similar magnitude.

In the CRA1 document (comment #3), the company has described the process they used to extrapolate KEYNOTE-048 trial OS K-M data for the following comparisons:

1. oral: pembrolizumab monotherapy (n=75) versus cetuximab+PLAT+5-FU (n=80)
2. oral: pembrolizumab+PLAT+5-FU (n=77) versus cetuximab+PLAT+5-FU (n=73)
3. non-oral: pembrolizumab monotherapy (n=182) versus cetuximab+PLAT+5-FU (n=175)
4. non-oral: pembrolizumab+PLAT+5-FU (n=165) versus cetuximab+PLAT+5-FU (n=162).

The company employed an accepted curve fitting approach. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) test statistics were used to provide an indication of the degree to which parametric distributions fitted the KEYNOTE-048 trial K-M data.

The company concluded that the log-normal distribution was the most appropriate distribution to use to extrapolate trial data. Whilst the company's approach to choosing a distribution was reasonable, the ERG cautions that this distribution leads to the situation where the mortality hazard becomes lower than that of the general population. This situation seems unlikely for a population with advanced or metastatic cancer. The ERG's and the AC's preferred distribution for the OS K-M data is the Weibull distribution.

Whilst PFS and time to treatment discontinuation (TTD) were not discussed in the CRA1, examination of the updated economic model that accompanied the CRA1 shows that PFS and TTD were modelled using the oral and non-oral subgroup data. The approaches used by the company are provided in

Table 1.

Table 1 Distributions used by the company to model PFS and TTD

	PFS	TTD
Pembrolizumab monotherapy	Hybrid exponential; 52-week cut off	KEYNOTE-048 trial TTD K-M data
Pembrolizumab+PLAT+5-FU		
Cetuximab+PLAT+5-FU		
PLAT+5-FU	Company NMA	Constant hazard applied to PFS data; maximum duration of treatment=18 weeks

PFS=progression free survival; K-M=Kaplan-Meier; NMA=network meta-analysis; TTD=time to treatment discontinuation
Source: company model accompanying CRA1

2.3 Utility values for post-progression health state

NICE request #4: *Provide an alternative utility value for progressed disease. This should come from published literature*

The NICE AC considered that the utility value used by the company to represent the health-related quality of life of patients in the progressed disease health state (0.71) was too high. The company attempted to address this concern by using an alternative value identified from the literature (0.66).[3] The ERG recognises that the company was seeking a lower value in response to an AC concern; however, the ERG considers that the method used to choose this utility value was arbitrary and there is no reason to consider that it is any more robust than the value estimated using data from the KEYNOTE-048 trial (0.71). Further, the ERG considers that, given that the company used time to death utility decrements within their model, the AC has misinterpreted the actual values that would apply to people in the progressed disease health state. Using a Weibull extrapolation of KEYNOTE-048 trial OS K-M data and 5-year treatment waning, the time to death decrements lead to the utility values displayed in Table 2.

Table 2 Company model progressed disease health state utility values

Period before death (days)	Utility values applied in original company model	Utility values applied in new company model
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: company model accompanying CRA1

2.4 Additional cost effectiveness analyses

NICE request #5: *Explore techniques to provide full incremental analyses for the two subgroups. The incremental analysis should incorporate all of the above, a 2-year stopping rule, and a 5-year duration of treatment effect. In addition, carry out alternative analyses using the company's fractional polynomial network meta-analysis and the ERG's approach of using data from the KEYNOTE-048 trial for the comparison of pembrolizumab+PLAT+5-FU*

A fully incremental analysis was not conducted by the company. The company's justification for not providing a fully incremental analysis is provided in CRA1 comment #5 and is based on their interpretation of the NICE Methods Guide.[4] The company considers that a fully incremental analysis in not appropriate as neither pembrolizumab monotherapy nor pembrolizumab+PLAT+5-FU are established practice or recommended by NICE.

The company generated cost effectiveness results for the oral and non-oral subgroups using their preferred PFS, OS and TTD extrapolations (CRA1 Table 1 to Table 10). The company presented results using their original (starting) progressed disease health state utility value (0.71) and also the alternative (started) progressed disease health state utility value (0.66). The ERG was able to verify the majority of results produced by the company; however, two discrepancies were identified (see Appendix A.2 for details).

The ERG's preferred analyses/results remain those provided in the confidential appendix to the original ERG report.

However, in line with NICE's request, the ERG has generated new cost effectiveness results (Table 3 to Table 8) based on the AC's preferred scenario (without any adjustments for baseline characteristics between treatment arms for the oral and non-oral subgroups), namely:

- modelling of OS, PFS and TTD for the oral and non-oral subgroups separately, using oral and non-oral subgroup data from the KEYNOTE-048 trial
- 2-year stopping rule
- Weibull extrapolation of OS data for all sets of data
- 5-year duration of pembrolizumab treatment effect
- the lower utility value for the progressed disease health state (0.66) identified by the company.

This version (V2) of the ERG's response to ACD1 includes updated tables (Table 3, Table 4 to Table 8) as a result of fixing errors that were identified after the second PMB:

- the PAS discount for pembrolizumab had been applied to the cost of cisplatin
- PLAT+5-FU had been selected as the comparator in the model to generate results for non-oral cavity subgroup when cetuximab+PLAT+5-U should have been chosen as the comparator.

The ERG's concerns relating to these new analyses have already been described within this report and can be summarised as follows:

- use of subgroup data (under-powered post-hoc analysis)
- the AIC/BIC evidence relating to the fit of the distributions to KEYNOTE-048 trial OS K-M data (all-comers population, oral subgroup and non-oral subgroup)
- utility values used to represent patient HRQoL in the progressed disease health state.

Table 3 Company base case and NICE Appraisal Committee preferred base case: oral patients – pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (discounted price of pembrolizumab, list prices for other drugs)

Scenario/ERG amendment	Pembrolizumab+PLAT+5-FU			Cetuximab+PLAT+5-FU			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company post ACD base case	***£56,184***	***1.238***	***1.810***	***£60,193***	***1.412***	***0.987***	***-£4,009***	***0.397***	***0.251***	***Dominant***	
B. Committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) with adjustment for treatment switching	**£55,769**	**1.176**	**1.711**	**£60,193**	**0.987**	**1.412**	**-£4,424**	**0.188**	**0.298**	**Dominant**	**-**
C. Committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) with no adjustment for treatment switching	**£54,954**	**1.072**	**1.543**	**£56,520**	**0.913**	**1.290**	**-£1,566**	**0.159**	**0.253**	**Dominant**	**-**

ACD=Appraisal Committee Determination; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life years

Table 4 Company base case and NICE Appraisal Committee preferred base case: oral patients – pembrolizumab versus cetuximab+PLAT+5-FU (discounted price of pembrolizumab, list prices for other drugs)

Scenario/ERG amendment	Pembrolizumab			Cetuximab+PLAT+5-FU			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company post ACD base case	***£41,309***	***1.172***	***1.730***	***£60,193***	***0.987***	***1.412***	***-£18,883***	***0.18***	***0.317***	***Dominant***	
B. Committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) with adjustment for treatment switching	**£41,134**	**1.142**	**1.682**	**£60,193**	**0.987**	**1.412**	**-£19,059**	**0.155**	**0.269**	**Dominant**	**-**
C. Committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) with no adjustment for treatment switching	**£40,466**	**1.020**	**1.484**	**£56,520**	**0.913**	**1.290**	**-£16,054**	**0.107**	**0.193**	**Dominant**	**-**

ACD=Appraisal Committee Determination; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life

Table 5 Company base case and NICE Appraisal Committee preferred base case: non-oral patients – pembrolizumab+PLAT+5-FU versus PLAT+5-FU (discounted price of pembrolizumab, list prices for other drugs)

Scenario/ERG amendment	Pembrolizumab+PLAT+5-FU			PLAT+5-FU			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£62,676***	***1.661***	***2.430***	***£21,913***	***0.790***	***1.129***	***£40,763***	***0.870***	***1.301***	***£46,836***	
B. Committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) with adjustment for treatment switching	**£61,100**	**1.450**	**2.098**	**£21,758**	**0.768**	**1.094**	**£39,342**	**0.682**	**1.003**	**£57,673**	**+£10,837**
C. Committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) with no adjustment for treatment switching	**£61,056**	**1.445**	**2.089**	**£22,002**	**0.806**	**1.151**	**£39,053**	**0.640**	**0.938**	**£61,067**	**+£14,231**

ACD=Appraisal Committee Determination; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life

Table 6 NICE Appraisal committee preferred base case: non-oral patients – pembrolizumab versus PLAT+5-FU (discounted price of pembrolizumab, list prices for other drugs)

Scenario/ERG amendment	Pembrolizumab			PLAT+5-FU			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£49,304***	***1.473***	***2.139***	***£21,913***	***0.790***	***1.129***	***£27,391***	***0.683***	***1.010***	***£40,121***	
B. Committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) with adjustment for treatment switching	**£48,166**	**1.273**	**1.826**	**£21,758**	**0.768**	**1.094**	**£26,408**	**0.505**	**0.732**	**£52,307**	**+£12,186**
C. Committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) with no adjustment for treatment switching	**£48,143**	**1.270**	**1.822**	**£22,002**	**0.806**	**1.151**	**£26,140**	**0.464**	**0.670**	**£56,289**	**+£16,168**

ACD=Appraisal Committee Determination; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life

Table 7 Incremental analysis for oral cavity patients (adjusted for treatment switching) – committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) (discounted price of pembrolizumab, list prices other drugs)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER per QALY gained
Pembrolizumab monotherapy	**£41,134**	**1.142**			
Pembrolizumab+PLAT+5-FU	**£55,769**	**1.176**	**£14,635**	**0.034**	**£430,441***
Cetuximab+PLAT+5-FU	**£60,193**	**0.987**	**£4,424**	**-0.189**	**Dominated**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life

*Estimated by ERG, not from model

Table 8 Incremental analysis for non-oral cavity patients (adjusted for treatment switching) – committee preferred scenario (Weibull OS extrapolation, 2-year stopping rule, 5-year duration of treatment effect, lower progressed disease utility) (discounted price of pembrolizumab, list prices other drugs)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER per QALY gained
PLAT+5-FU*	**£21,758**	**0.768**			
Pembrolizumab monotherapy	**£48,166**	**1.273**	**£26,408**	**0.505**	**£52,307**
Pembrolizumab+PLAT+5-FU	**£61,100**	**1.450**	**£12,934**	**0.177**	**£73,073****

*Estimate of PLAT+5-FU with highest QALYs used (pembrolizumab monotherapy vs PLAT+5-FU)

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life

**Estimated by ERG, not from model

2.5 Points relating to company NMAs (CRA1 comments #7 & #8)

Within the CRA1 document (comment #7), the company highlighted a misinterpretation of the ERG's opinion relating to how the company had described their NMA methods (ACD1, section 3.7). The ERG can confirm that the methods described by the company during the technical engagement period were appropriate.

Company CRA1 comment #8, contests the AC view (ACD1, section 3.7) that the company's NMA approach may overestimate the effectiveness of pembrolizumab (as monotherapy or in combination with PLAT+5-FU) and refers the AC to the company's technical engagement response.

The critique of the company's NMAs that was provided in the original ERG report is reproduced for convenience in the Appendix A.3 of this report (Box 1). In summary, the ERG's conclusion was (and remains) that the company's NMAs did not provide any reliable evidence for the comparison of pembrolizumab (monotherapy or with PLAT+5-FU) versus either of the relevant comparators, in either of the patient populations.

2.6 NICE end of life criteria

Table 9 summarises the estimated life expectancy for patients treated with pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU for the oral subgroup, and Table 10 summarises the estimated life expectancy for patients treated with pembrolizumab, pembrolizumab+PLAT+5-FU and PLAT+5-FU for the non-oral subgroup. In all cases, survival with current standard of care is less than 24 months and the gain in life expectancy for the comparison of pembrolizumab (as monotherapy or in combination with PLAT+5-FU) is greater than 3 months when compared to cetuximab+PLAT+5-FU for the oral subgroup or when compared to PLAT+5-FU for the non-oral subgroup.

Table 9 End of Life estimates for oral patients

Treatment	Distribution to extrapolate pembrolizumab	Mean life expectancy (months)	Gain in life expectancy with pembrolizumab (months)
Pembrolizumab			
Cetuximab+PLAT+5-FU	Log-normal (company preferred)	[redacted]	
Pembrolizumab		[redacted]	[redacted]
Cetuximab+PLAT+5-FU	Weibull (committee preferred)	[redacted]	
Pembrolizumab		[redacted]	[redacted]
Pembrolizumab+PLAT+5-FU			
Cetuximab+PLAT+5-FU	Log-normal (company preferred)	[redacted]	
Pembrolizumab+PLAT+5-FU		[redacted]	[redacted]
Cetuximab+PLAT+5-FU	Weibull (committee preferred)	[redacted]	
Pembrolizumab+PLAT+5-FU		[redacted]	[redacted]

Source: company model accompanying CRA1 and ERG analysis with Weibull OS extrapolation

Table 10 End of Life estimates for non-oral patients

Treatment	Distribution to extrapolate pembrolizumab	Mean life expectancy (months)	Gain in life expectancy with pembrolizumab (months)
Pembrolizumab			
PLAT+5-FU	Log-normal (company preferred)	[redacted]	
Pembrolizumab		[redacted]	[redacted]
PLAT+5-FU	Weibull (committee preferred)	[redacted]	
Pembrolizumab		[redacted]	[redacted]
Pembrolizumab+PLAT+5-FU			
PLAT+5-FU	Log-normal (company preferred)	[redacted]	
Pembrolizumab+PLAT+5-FU		[redacted]	[redacted]
PLAT+5-FU	Weibull (committee preferred)	[redacted]	
Pembrolizumab+PLAT+5-FU		[redacted]	[redacted]

Source: company model accompanying CRA1 and ERG analysis with Weibull OS extrapolation

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APPENDICES

Appendix A.1: Comparative overall survival data

Figure 3 Keynote-048 trial Kaplan-Meier overall survival data for patients receiving cetuximab+PLAT+5-FU (versus pembrolizumab+PLAT+5-FU)

Source: Company model submitted in response to the first ACD

Figure 4 Keynote-048 trial progression-free survival data for patients treated with cetuximab+PLAT+5-FU (versus pembrolizumab+PLAT+5-FU)

Source: Company model submitted in response to the first ACD

Appendix A.2: ERG verification of company results

The ERG ran the analyses presented in Tables 1 to Table 10 of the CRA1 document. Discrepancies between the company results and those generated by the ERG relate to Table 2 and Table 6. The ERG versions of these tables are presented below and discrepancies between the company and ERG results are coloured blue.

Table 2 Pembrolizumab Combination Therapy Oral Cavity Subgroup ICER with Lower Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	56,184	1.81	1.24	-	-	-	-
EXTREME regimen	60,193	1.41	0.99	-4,009	0.40	0.25	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Source: company response to ACD1

Table 6 Pembrolizumab Combination Therapy Oral Cavity Subgroup ICER with KN048 Post-Progression Utility Value

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	56,184	1.81	1.28	-	-	-	-
EXTREME regimen	60,193	1.41	1.01	-4,009	0.40	0.26	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Source: Company response to ACD1

Appendix A.3: ERG critique of company NMAs

Box 1 ERG critique of the company's network meta-analysis (copy from original ERG report)

4.6.9 ERG critique of the company's network meta-analysis

Generally, the ERG considers that the company's methodological approach to performing NMAs is appropriate and the ERG agrees that it is not suitable to summarise effectiveness for pembrolizumab (monotherapy or with PLAT+5-FU) in comparison with cetuximab+PLAT+5-FU or PLAT+5-FU using HRs that remain constant over time. Overall, the NMA results suggest that benefit from treatment with pembrolizumab (monotherapy or with PLAT+5-FU) in comparison to cetuximab+PLAT+5-FU or PLAT+5-FU is often not seen in the early stages of treatment. In fact, cetuximab+PLAT+5-FU was shown to statistically significantly improve PFS in comparison to pembrolizumab monotherapy in the early stages of treatment (month 1 to month 3).

The ERG has concerns about the usefulness and validity of the results of the company's NMAs. Firstly, the company states that they considered the plausibility of the HRs estimated by the FP models as part of the model selection process (Appendix D to the CS, p61), however no assessments of plausibility were provided in the CS and therefore the ERG is uncertain regarding the clinical plausibility of the results of the NMAs. Furthermore, the company states that they assessed two categories of second order FP models that assume 1) treatment only has an impact on two of the three hazard function parameters over time, and 2) treatment has an impact on all three hazard function parameters over time (Appendix D to the CS, p60). However, no information is provided in the CS on how these two categories of FP models were assessed. According to the methods described by Jansen,[36] treatment has an impact on all three hazard function parameters for all second order fractional polynomial models. Therefore, the ERG is unsure whether the second order FP models presented in the CS have been estimated correctly.

Furthermore, for the KEYNOTE-048 trial, the company used data from the PD-L1 CPS≥1 subgroup of patients; for all other trials, the company used data from the overall trial populations. The ERG considers that this approach is likely to have introduced heterogeneity into the NMAs.

Finally, the company's NMAs do not provide results that are stratified by primary tumour location: oral cavity versus non-oral cavity. The majority of trials included in the NMAs include both patients with oral cavity cancer and non-oral cavity cancer (see Section **Error! Reference source not found.** of this ERG report). Treatment with cetuximab+PLAT+5-FU is recommended by NICE for patients with R/M HNSCC whose cancer originated in the oral cavity. Clinical advice to the ERG suggests that the SoC for all other patients (non-oral cavity patients) with R/M HNSCC is treatment with PLAT+5-FU only.

Source: Original ERG report (pp80-81)