NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck (review of TA172)

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Merck

   Please note notification of no comments was received from the Department of Health

3. **ERG critique** from Liverpool Reviews & Implementation Group (LRIG)

4. **Commercial Access Agreement**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck

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

Definitions:

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

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

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

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Merck	**Executive Summary** Merck welcomes the opportunity for ongoing discussions about cetuximab in combination with platinum-based chemotherapy for a subgroup of patients with recurrent/metastatic cancer of the head/neck. Cetuximab is the standard of care for patients with this diagnosis who have no treatment alternatives beyond chemotherapy and oral cavity patients are recognised as a group with a particularly high unmet need. Cetuximab's efficacy in patients with oral cavity tumours was confirmed in a pre-defined subgroup analysis in the EXTREME trial. There is a strong biological rationale for the greater efficacy seen in this group than in the overall population. Oral tumours over-express EGFR and it follows that an EGFR inhibitor would therefore have more activity. Related to its chimeric structure, cetuximab also has an immunotherapeutic action. Together these mechanisms contribute to cetuximab's efficacy in both the pre and post progression state. The trend towards greater efficacy in this subgroup is validated by results of panitimumab's SPECTRUM trial and is confirmed in our analysis of 5 year data. Collectively this evidence confirms that the subgroup findings are unlikely to be an artefact and on that basis, the treatment meets end of life criteria in patients with tumours in the oral cavity. For the assessment of cost-effectiveness, we: • incorporate the five year survival data and a more complete assessment of the oral cavity subgroup • utilise a trial-based model in the base case given the maturity of the survival data in the EXTREME trial • revise the price of cetuximab, increasing the level of the simple discount from [redacted]% to [redacted]%. The results of the trial-based model, incorporating the revised discount, confirm that cetuximab is a cost-effective treatment when added to platinum-based chemotherapy. The ICER, under a weekly dosing assumption, being £[redacted]/QALY. In clinical practice, cetuximab is more commonly delivered less frequently (every two or three weeks). As per the NICE methods guide, it is appropriate for the Committee to take into account real life use of the drug in their deliberations and cetuximab's dose has been discussed in depth in the mCRC appraisal running in parallel in which the Committee are accounting for real world costs. In this economic model, the ICER reduces considerably to £[redacted]/QALY when accounting for how cetuximab is actually used in the NHS. Overall, the	Thank you for your comments. The committee considered in detail all of the comments and evidence received after consultation and the discussions are presented in sections 4.13–4.24 of the FAD. We draw your attention in particular to sections of the FAD noted below, relating to the specific issues raised.

Consultee	Comment [sic]	Response
	Committee can be confident that they are not being asked to make a judgement at the margins cost-effectiveness. Cetuximab offers value for money to the NHS as a treatment for patients with a severe, debilitating tumour with no alternative therapies beyond chemotherapy.	
Merck	**1 Clinical effectiveness** **1.1 Clinical validity of oral cavity subgroup** The Committee acknowledged the high unmet need of patients with RM-SCCHN with tumours in the oral cavity. This was on the basis of expert clinical opinion and the evidence that was provided in our resubmission in May 2016, discussed during the first meeting in September 2016. This patient group have a poorer prognosis than patients with tumours in other locations and, in common with the whole population, no alternative treatment options apart from platinum-based chemotherapy. The Committee, however, have some concerns about the validity of the data in the oral cavity subgroup (from the EXTREME trial) which we discuss in the following section. **1.2 Validity of the results (from the EXTREME trial) in the oral cavity subgroup** We recognise the Committee's concern about the efficacy results that are derived from this small population (n=88) and we hope the following justifications will reassure the Committee of its legitimacy: • **The subgroup analyses were pre-defined and are confirmed by long-term follow up data** The hazard ratio for death in the previous analysis (where median follow-up was 19.1 months in the cetuximab group and 18.2 months in the chemotherapy-alone group) was 0.42 (95% CI 0.26 to 0.67) and in the analysis at the five-year follow up was [redacted]. • **There is a strong biological plausibility for the additional benefit observed in the oral cavity subgroup** High epidermal growth factor receptor (EGFR) levels are found in the majority of H&N cancers, it has been specifically evaluated in oral cavity SCCHN. EGFR overexpression has been demonstrated in oral cavity tumours and, in turn, this has been shown to correlate with, and predict poor prognosis for these patients in a number of studies (Sheu, 2009; Laimer, 2007; Storkel, 1993; Thomas, 2012). • **Comparable results are seen with panitumumab (another EGFRi) in oral cavity patients with a low probability that this is due to chance** Panitumumab has been studied in both locally advanced and recurrent/metastatic head and neck cancer too. The panitumumab trial – SPECTRUM (Vermorken, 2013) – shows a similar trend in magnified benefit in patients with tumours of the oral cavity to that observed in the EXTREME study with cetuximab, see Figure 1 and Figure 2. PFS was significantly improved in the patient subgroup in both the EXTREME and SPECTRUM trials, with better HRs in each compared with the results seen in the ITT populations [ITT EXTREME (PFS HR: 0.54, 95% CI 0.43 – 0.67) and ITT SPECTRUM study (PFS HR: 0.78, 95% CI 0.66 – 0.92)]. A similar trend holds with overall survival with a significant improvement in OS in the oral	See sections 4.15 and 4.17 of the FAD.

Consultee	Comment [sic]	Response
	cavity subgroup in EXTREME, confirmed (albeit not significant) by the SPECTRUM study. In both cases, the HRs are improved compared with the results seen in the respective overall populations in each trial [ITT EXTREME (OS HR: 0.80, 95% CI 0.64 – 0.99) and ITT SPECTRUM study (OS HR 0·87, 95% CI 0.73 – 1.04)]. This evidence demonstrates the differential sensitivity to EGFR inhibition in a tumour where EGFR expression is amplified and confirms that the improved outcomes for patients with oral tumours is clinically driven, rather than being a chance finding. Cetuximab has immunotherapeutic properties too and, as a chimeric (part mouse, part human) IgG1 antibody, has been shown to activate antibody dependent cellular cytotoxicity (ADCC). It activates the immune system to recruit natural killer cells which have the ability to lyse tumour cells (Rivera, 2008). The dual mechanism of action of cetuximab may contribute to the efficacy of cetuximab both in the pre- and post- progression state and a resultant improvement in overall survival and may help explain the observed differences in outcomes between cetuximab and panitimumab as outlined in the rational above. Figure 1: Subgroup analyses from the SPECTRUM study (Vermorken, 2013). *Figure 1 was presented, but is not replicated here. See committee papers.* Figure 2: Subgroup analyses form the EXTREME study (Vermorken, 2008). *Figure 2 was presented, but is not replicated here. See committee papers.*	
Merck	**1.3 The place of cetuximab in the treatment of head and neck cancer patients** The 'EXTREME' regimen is considered standard of care in international guidelines such as those produced by NCCN and ESMO (NCCN 2016, Gregoire 2010, Parikh 2016). In the recent update to the NCCN guidelines cetuximab with platinum-based chemotherapy (EXTREME regimen) remains the only category 1 recommendation for patients with first line RM SCCHN (NCCN guidelines 2016). Moreover, in a recent review of treatment options for RM SCCHN in the Journal of Clinical Oncology 2015 they stated that "The only regimen to demonstrate survival superiority is platinum, 5 FU and cetuximab" (Sacco, 2015). As a result, several ongoing phase III immune-oncology trials in 1st line RM SCCHN (patients who are untreated for recurrence and/or metastasis) utilise cetuximab plus platinum-based chemotherapy as the comparator, confirming its place as the established standard of care across the world. These are: • CHECKMATE 651 - Phase III trial in 490pts – nivolumab plus ipilumumab versus EXTREME (NCT02741570) • KEYNOTE 048 – Phase III trial in 825pts – pembrolizumab plus platinum plus 5FU versus pembrolizumab versus EXTREME (NCT02358031) • KESTREL – Phase III trial in 760pts – durvalumab plus tremelimumab verus durvalumab versus EXTREME (NCT02741570)	See sections 4.14 and 4.15 of the FAD.

Consultee	Comment [sic]	Response
	In oral cavity RM SCCHN, a specific subset of the disease with a particularly poor outcome, the benefit of cetuximab relative to platinum-based chemo is magnified, providing patients with 6 months of extra survival. Based on a protocol-defined subgroup analysis, the Committee can be confident that the results represent the effect of cetuximab in this patient population. We urge the panel to approve cetuximab in this setting, so that patients with limited treatment alternatives and poor prognosis can continue to receive benefit from this treatment. In summary: • Patients with tumours of the oral cavity have a high unmet need as these tumours tend to be larger and cause significant burden to patients who have a worse prognosis in terms of survival and quality of life. • There is a clear biological rationale as to why EGFR inhibitors would have a greater effect on oral cavity tumours as these have a reported increase in EGFR receptors therefore would be expected to be more sensitive to EGFR inhibition. • The subgroup analyses of 2 phase III trials of EGFR inhibitors showed a clear OS and PFS benefit in this patient subgroup in pre-planned analyses, and the oral cavity subgroup derived the most benefit of all subgroups in both trials.	
Merck	**2 Health Economics** **Summary of Health Economics section** In brief, five-year survival data for the oral cavity subgroup of the EXTREME trial are very mature; only two patients are censored in the PFS analysis and three in the OS analysis. Therefore, we present a trial-based analysis as the base case assessment of the cost-effectiveness of cetuximab. This immediately removes any uncertainty associated with extrapolation which, as we show in a scenario analysis, is somewhat arbitrary. In our base case model, the cost inputs are derived as follows: • Costs of treatment are a product of the average total number of whole vials delivered to patients in the EXTREME trial and the unit cost of a vial; by using actual trial data we avoid the need to retrospectively apply a correction to predicted doses when the model doesn't match the actual trial doses (i.e. a 'dose-intensity' correction) • Treatment-related costs (i.e. resource use associated with administration) are a product of the average number of dosage sessions per treatment per patient and the cost per session (itself a product of the resource use and cost) • Costs of adverse events are estimated as a product of the 'interventions' associated with adverse events and the unit cost of each 'intervention' • Non treatment-related health state costs are estimated as in the previous model by applying a weekly PFS and PPS cost for time spent in each of those health states. Efficacy (QALYs) over the five year horizon is estimated as the product of time in progression free and time in post-progression and the utilities associated with each state. When real world dosing patterns are accounted for in the economic model, cetuximab is a cost-	Thank you for your comments. The committee considered in detail all of the comments and evidence received after consultation and the discussions are presented in sections 4.13–4.24 of the FAD. We draw your attention in particular to sections of the FAD noted below, relating to the specific issues raised.

Consultee	Comment [sic]	Response
	effective treatment option for patients with tumours of the oral cavity versus chemotherapy alone. The ICER in this analysis is £[redacted]/QALY. When 100% weekly dosing is assumed, the ICER is £[redacted]/QALY. In a scenario analysis in which an extrapolation based model is used, the deterministic ICER assuming 100% weekly dosing is £[redacted]. The PSA analysis aligns with this giving an ICER of £[redacted]/QALY. When real world dosing patterns are accounted for, the ICER falls to is £[redacted]/QALY. In summary, two robust analyses confirm that cetuximab is a cost-effective treatment option for patients with tumours of the oral cavity. The ICERs are well below the cost-effectiveness threshold for an end-of-life medicine and the Committee can be reassured that they are not making a decision at the margins of cost-effectiveness.	
Merck	**2.1 Revised base case analysis** In preparation for this resubmission, Merck have spent considerable time debating the appropriate approach to the economic model. We had previously intended to update the existing Excel-based economic model with the latest survival data from the EXTREME trial, update the extrapolations and tailor the model to the oral cavity subgroup as much as possible. Upon further analysis we have determined that, in the context of the latest data from the EXTREME study, extrapolation of the survival data is unnecessary and introduces complexity and uncertainty. We are therefore presenting a trial based analysis as the base case to address the decision problem in this re-appraisal. We are not submitting this as an Excel model, but instead walk the ERG through its inputs in the remainder of the document. The primary rationale for this approach is the maturity of the survival dataset at five-year follow up in patients with tumours of the oral cavity. The tables below demonstrate this. Table 1: Progression free survival at five years in oral cavity subgroup in EXTREME trial. *Table 1 was presented, but is not replicated here. See committee papers.* Table 2: Overall survival at five years in oral cavity subgroup in EXTREME trial. *Table 2 was presented, but is not replicated here. See committee papers.* In our opinion, a trial-based model is the least controversial analysis given that it does not involve extrapolation and instead will censor those patients who are alive/progression-free at the end of the five-year period. The approach is likely to be conservative as, while it censors both benefits and costs from the assessment, the impact of censoring QALY gains will outweigh the impact of censoring costs as the censored patients at 5 years are likely to be long-term survivors. We conduct an extrapolation based model as a scenario analysis – as described in Section 2.8, however the selection of parametric curve fits for the data is arbitrary and we feel unable to justify projected survival gains on the basis of three surviving patients for all extrapolations except Weibull, which best fit the KM PFS and OS data to five years.	See section 4.13 and 4.16 of the FAD.

Consultee	Comment [sic]	Response
	2.2 Model structure Conceptually, the model structure remains the same. Figure 3: Conceptual model structure. *Figure 3 was presented, but is not replicated here. See committee papers.* The key model characteristics are: • Total progression-free time is derived directly from the individual patient data (IPD) as a simple per patient average of the total time spent in PFS using five year survival data from EXTREME. Average time in the post-progression survival (PPS) state is estimated by subtracting this from the mean per patient overall survival. • Patients receive cetuximab with cisplatin/carboplatin + (5-FU) or cisplatin/carboplatin + (5-FU) only when in the stable/response health state. Patients with 'progressive disease' receive palliative care, a mixture of various chemotherapy, surgery and radiation therapy as observed in the oral cavity subgroup in the EXTREME trial. • Comparator therapy is platinum-based chemotherapy regimens (5-Flurouracil combined with cisplatin) • NHS and PSS perspective • Five-year time horizon • Resource use and drug costs were updated in April to reflect the latest costs available using 2014/2015 NHS reference costs (NHS, 2014/15) for inpatient, outpatient and investigations; Personal Social Services Research Unit (PSSRU) 2015 for primary care costs and eMIT (June 2015) (eMIT, 2015) and BNF 71 (BNF, 2016) for drug costs. The cost of neutropenia was adjusted from 2012/13 to 2015 assuming 3.7% inflation for transfusions (OHE, 2012). **2.3 Cost of cetuximab** Merck have revised the discount on cetuximab's list price from [redacted]% to [redacted]%. The level of the discount remains commercial in confidence. We have received confirmation from the Department of Health that they are content with the revision and that this can be considered as part of the ongoing appraisals for cetuximab (this one and the ongoing mCRC MTA). **2.4 Inputs into the trial based model** There are three sets of inputs for both treatment arms that we require for the calculation of cost-effectiveness in the trial-based model: • Mean survival (progression-free and overall) • Total costs (treatment cost, administration cost, cost of adverse events, non-treatment related state costs) • Pre- and post-progression utilities We will not be presenting an Excel-based model for the trial based assessment. Instead, in the	

Consultee	Comment [sic]	Response
	following sections we will set out clearly and transparently how these three sets of inputs have been estimated for cetuximab+chemotherapy and for chemotherapy alone.	
Merck	**2.4.1 Mean survival** We analysed the five-year data in the oral cavity subgroup of the EXTREME trial, estimating the restricted mean progression-free and overall- survival at five years. The results are presented below in Figure 4, Figure 5 and Table 3. Consistent with the earlier data cut, progression free survival at five-year follow up was significantly improved in the cetuximab arm versus chemotherapy for patients with tumours of the oral cavity [redacted]. The same trend was seen with overall survival [redacted]. Figure 4: Kaplan-Meier data for progression free survival, oral cavity. *Figure 4 was presented, but is not replicated here. See committee papers.* Figure 5: Kaplan-Meier data for overall survival, oral cavity patients. *Figure 5 was presented, but is not replicated here. See committee papers.* The restricted mean survival times (days / years) in each arm is presented in Table 3. Table 3: Restricted mean survival (days) at five-years. *Table 3 was presented, but is not replicated here. See committee papers.* In summary, the survival inputs for the estimate of cost-effectiveness in this decision problem are: PFS: Cetuximab = [redacted] days | chemotherapy = [redacted] days OS: Cetuximab = [redacted] days | chemotherapy = [redacted] days	See section 4.16 of the FAD.
Merck	**2.4.2 Total costs** Costs in the analysis fall into one of four categories: • Treatment costs • Treatment related costs, e.g. administration • Costs of treating adverse events • Non-treatment related health state costs **2.4.2.1 Treatment costs** Lifetime treatment costs of cetuximab and chemotherapy comprise drug and administration costs. In the trial based model, the actual total number of whole vials delivered to patients in the EXTREME trial were estimated in order to avoid the requirement to implement a dose-intensity correction (this was controversial in the previous submission). Using the IPD, we quantified the total number of whole	See sections 4.19, 4.20 and 4.21 of the FAD

Consultee	Comment [sic]	Response
	vials per treatment utilised by patients. Results show in Table 4 suggest the average patient used the following vials of treatment during the EXTREME trial. Table 4: Total vials delivered to oral cavity patients in the EXTREME trial. *Table 4 was presented, but is not replicated here. See committee papers.* The average patient used [redacted] vials of cetuximab which can then be used to estimate the cost of cetuximab. The cost of cetuximab in the model is critical and we can validate the results of this approach with another. The cumulative dose of each treatment per patient in the EXTREME trial is represented in Table 5 below and the number of dosage sessions in Table 6. Table 5: Cumulative dose of each treatment received per arm in oral cavity subgroup patients at 5 years follow up. *Table 5 was presented, but is not replicated here. See committee papers.* Table 6: Total number of 'dosage' sessions in the EXTREME trial for oral cavity subgroup patients at five year follow up. *Table 6 was presented, but is not replicated here. See committee papers.* From these tables we can estimate the mean dose delivered per 'visit'. For cetuximab this is [redacted] / [redacted] dosages = [redacted] / dose, which – when accounting for wastage – is 3 cetuximab vials (100mg each). On the basis of 3 vials per dose, the total number of vials in [redacted] dosages is [redacted]. In general, a method such as the one we use here which relies on the trial data to reflect dose reductions and dose interruptions is the most accurate reflection of how the drug will be used in clinical practice. The alternative way to estimate total dose of cetuximab is to approximate the expected dose based on posology and apply a dose intensity/exposure correction (which itself is based on the ratio of expected (based on posology): actual (trial dose)). This is the approach that was taken in the previous submission, where a correction was applied to adjust the predicted proportion of patients receiving cetuximab at full dose versus the proportion of patients receiving full dose in the trial. We deem it more accurate to utilise the actual trial data (especially when long term data are available) rather than applying a correction in hindsight when the model doesn't match what the trial observed. Unit costs of the treatments in each arm are presented in Table 7. Table 7: Unit costs of cetuximab and chemotherapy vials. *Table 7 was presented, but is not replicated here. See committee papers.* Mean treatment costs on the basis of the actual vials and cost per vial are therefore as follows.	

Consultee	Comment [sic]	Response
	Table 8: Cost of treatments in cetuximab arm of EXTREME trial. *Table 8 was presented, but is not replicated here. See committee papers.* Table 9: Cost of treatments in chemotherapy arm of EXTREME trial. *Table 9 was presented, but is not replicated here. See committee papers.* **2.4.2.2 Treatment-related resource use costs** Treatment related resource use costs are estimated by quantifying the number of 'visits' in the EXTREME trial data for oral cavity patients receiving each of the treatments as laid out in Table 10 below. Table 10: Number of visits in oral cavity patients in the EXTREME trial. *Table 10 was presented, but is not replicated here. See committee papers.* The visits are then costed under the assumptions ratified in the previous economic model and sourced from Hopper et al, 2004, i.e. that a visit to receive chemotherapy containing 5FU consists of 4 days inpatient stay on a medical oncology ward and that a visit to receive cetuximab, cisplatin or carboplatin alone consists of an outpatient visit. These assumptions were described in the original submission and are not amended as they are not a subject of critique. Table 11: Resource use per visit (source: Hopper et al, 2004). *Table 11 was presented, but is not replicated here. See committee papers.* Inpatient stay in medical oncology ward per day is costed at £362, based on 2014/15 NHS reference costs for day case and regular Day/Night, SB15Z: Deliver subsequent elements of a chemotherapy cycle. The total cost for four days stay is therefore £1448. An outpatient drug administration visit is costed at £204, based on 2014/15 NHS reference costs for Chemotherapy, SB15Z: Deliver subsequent elements of a chemotherapy cycle. On the basis of these costs, total lifetime administration costs for patients receiving cetuximab and those receiving chemotherapy are £11,407 and £4,275 respectively. The detail of this estimate is shown in Table 12. Table 12: Estimating administration costs in trial-based model. *Table 12 was presented, but is not replicated here. See committee papers.* The implicit assumption when generalising the findings from use of this method to the NHS	

Consultee	Comment [sic]	Response
	perspective is that cetuximab is administered weekly (i.e. as in the EXTREME trial). As Merck described in the resubmission in May 2016, cetuximab is more commonly administered on a different schedule. Data collected from the UK health care setting showed that while some patients are given cetuximab weekly (45%) over 50% of patients receive cetuximab as either a fortnightly infusion (22%) or once every three weeks, in line with chemotherapy (33%) (Data on File: Instar, June 2015). As such, these projections of administration costs are likely to be over-estimates of real world administration costs and consequently the projected ICERs in the trial based model are conservative. We approximate that the administration costs are overestimated by 30% (£11,407 versus £8,060[1]) based on a weighted average of the administration costs in a scenario where the market research assumption is used). [1]Estimated on the basis of a weighted average (as per market research on real world dosing) of total treatment related costs by revising Table 12 for fortnightly and three weekly dosing assumptions. **2.4.2.3 Costs of adverse events** In the patient-level EXTREME trial database, the treatment of adverse events is captured as one of several 'interventions': • None • Chemotherapy discontinued • Chemotherapy dose reduction • Chemotherapy delayed • Concomitant meds given • New or prolonged hospitalisation • Procedural surgery We have quantified how many of these events were applied to patients in the oral cavity subgroup in EXTREME over the five year follow up. Discontinuations and times of initiating concomitant medications are not counted if they are on the same day as another discontinuation or prescription. Hospitalisations are not counted if they are within two days of another hospitalisation. Table 13: Total interventions in response to adverse events in oral cavity subgroup of EXTREME trial. *Table 13 was presented, but is not replicated here. See committee papers.* Table 14: Number of interventions per patient in response to adverse events in oral cavity subgroup of EXTREME trial. *Table 14 was presented, but is not replicated here. See committee papers.* Table 15: Unit costs of interventions associated with experience of adverse event.	

Consultee	Comment [sic]	Response
	Table 15 was presented, but is not replicated here. See committee papers. Total costs of adverse events can therefore be estimated given the inputs above. This is reflected in Table 16. Table 16: Total costs of treating adverse events in patients with oral cavity tumours. *Table 16 was presented, but is not replicated here. See committee papers.* **2.4.2.4 Non-treatment related health state costs** The final category of costs contributing to the estimate of cost-effectiveness are treatment-independent costs within each health state. Given that many of these costs may be unobserved/unmeasured in the clinical trial itself, we defer to the expert clinical advice given in the previous submission to derive them. These costs were not subject to criticism by the ERG and were updated in May 2016 for the original CDF resubmission as follows. Table 17: Resource use and cost by health state (independent of treatment) every 3 weeks. *Table 17 was presented, but is not replicated here. See committee papers.* To estimate the treatment unrelated costs in each health state in the trial, we applied these weekly state costs to the time in each health state (as described in Table 3). Treatment unrelated costs per treatment arm are therefore as follows. *The table was presented, but is not replicated here. See committee papers.* Total treatment cost have been estimated for both cetuximab treated and chemotherapy treated patients above. The costs are summarised as follows: Cetuximab: • Treatment cost: £[redacted] • Treatment related costs: £11,407 • Adverse events: £2,754 • Treatment unrelated health state costs: £4,881 Chemotherapy: • Treatment cost: £149 • Treatment related costs: £4,275 • Adverse events: £2,333 • Treatment unrelated health state costs: £2,510 In summary, the cost inputs for the estimate of cost-effectiveness in this decision problem are:	

Consultee	Comment [sic]	Response
	Cetuximab = £[redacted] Chemotherapy = £9,267	
Merck	**2.4.3 Utilities** Utilities for this updated model were derived using the same method as developed for the original submission (NB: the mapping to utilities was not an area of critique and has therefore not been modified). To obtain utility estimates for the PFS and PPS health states, QLQ-C30 scores from the oral cavity subgroup patients only in the EXTREME trial were mapped onto the EQ-5D scores using an algorithm previously developed by Kind et al 2005. **EQ-5D = 0.633 + 0.047*Q29 - 0.124*Q3 -0.167*Q5 -0.086*Q11 -0.102*Q20 -0.082*Q26** The QLQ-C30 scores for the stable/responsive state and progressive/disease state were calculated from the oral cavity data in the EXTREME trial and the utility scores were calculated using the above regression equation. This method is the same as that used in the previous submission. It was not previously challenged and has therefore not been revised for this submission. Treatment specific values are utilised in the stable/responsive health state in order to capture the differences in quality of life during active treatment caused by either benefit from treatment or resulting from the adverse effects of treatment. Merck believe that the assumption that cetuximab has a positive effect on quality of life is justified by the EXTREME trial evidence in all patients: 1. Data from EXTREME: there was a significant improvement in the global health status/QoL score in the cetuximab arm (p=0.0415). Symptom scores for problems associated with reduced sexuality, social contact, pain, swallowing, speech, sense problems and social eating all improved in the cetuximab arm, showing the QoL benefit resulting from the significant tumour shrinkage activity of cetuximab. The improvements in swallowing and pain reached statistical significance (p=0.0162 and p=0.0027, respectively) (Mesia, 2010). 2. The best overall response rate for the oral cavity subgroup was 46.5% in the EXTREME trial highlighting the efficacy of tumour shrinkage treatment in this group. This response to treatment measured by reduction in tumour size in a population who are associated with bulky tumours in the mouth region will inevitably have a beneficial impact on patients QoL at the pre-progression “stable/ responsive” disease health state. Additionally a number of UK H&N oncologists consulted by Merck confirmed that treatment with cetuximab does indeed improve patients’ QoL. Expert testimony noted that ‘better response means less disease related symptoms means clinical benefit and better QoL’. Another consultant noted that the improvement in time to progression of the disease (PFS) can also be used as a proxy for	See section 4.18 of the FAD.

Consultee	Comment [sic]	Response
	patients' improvement in their quality of life, and in this case this improvement was 3.3 months beyond that of chemotherapy alone. Another consultant stated that there is improvement in patients' quality of life, 'particularly as oral cancer is impacted by eating/chewing etc. prevents wearing of dentures'. Cetuximab significantly reduces the size of tumours in the oral cavity and therefore can be inferred to improve the lives of patients. The results of the utility mapping exercise are represented fully in the table below: *The table was presented, but is not replicated here. See committee papers.* Table 18 below summarises the utility inputs into the estimate of cost-effectiveness for cetuximab. Table 18: Utility values utilised in the economic model When these QALYs are applied to the mean survival data in the EXTREME trial, as described in Table 3, the total QALYs in each treatment arm can be estimated. Table 19: QALYs accruing in each health state in each treatment arm	
Merck	**2.5 Cost-effectiveness of cetuximab** Using the inputs described in Section 2.4.1, Section 2.4.2 and Section 2.4.3, the cost-effectiveness of cetuximab as a treatment for patients with R/M SCCHN tumours of the oral cavity can be estimated. Table 20: Costs associated with cetuximab treatment in oral cavity patients Table 21: Efficacy (QALY) gains associated with cetuximab in oral cavity patients Therefore the cost-effectiveness of cetuximab versus chemotherapy for patients with recurrent/metastatic oral tumours is £[redacted], however this analysis assumes weekly dosing. When real world dosing is accounted for, i.e. a weighted average of weekly, fortnightly or less, as suggested by the market research described in Section 2.4.2.2, treatment related costs for cetuximab fall to £[redacted] and consequently the ICER falls to £[redacted]. In conclusion, the treatment is cost-effective under the assumptions of an end of life treatment, which we believe to be justified by the trial evidence. **2.6 Sensitivity analysis** A sensitivity analysis was undertaken in the trial-based model. Uncertainties surrounding the cost effectiveness in the trial based analysis are assessed following the approach as introduced by van Hout et al (1994)[2]. In this approach we used the total per patient costs (here the sum of drug costs, cost of associated care, costs of adverse events and the costs of non-treatment-associated care) and the total per patient effects (here QALYs) and estimated the difference between both arms in these parameters. Using the mean differences and the standard errors around the means we modelled	See sections 4.18. 1.19, 4.20 and 4.21 of the FAD.

Consultee	Comment [sic]	Response
	these as a result of a bivariate normal distribution taking the covariance between individual cost and effects as an estimate of the correlation between mean costs and mean effects. Figure 6 shows the results, where the outer ellipse defines the smallest area holding 95% of the probability density, the middle ellipse defines the smallest area holding 50% of the probability density and the inner ellipse and the smallest area with 5% of the probability density. It is noted that this approach only acknowledges the variation in volumes of resource use and the variation in survival (pre and post progression) and disregards the uncertainty surrounding the estimates of unit costs or the uncertainty surrounding the quality of life scores in pre and post progression states. [2]Van Hout BA, M Al, GS Gordon, FFH Rutten. Costs, effects and C/E-ratio's alongside a clinical trial. Health Economics, 1994, 3, 309-319. Figure 6: Cost-effectiveness plane - cost-effectiveness of cetuximab in oral cavity patients. *Figure 6 was presented, but is not replicated here. See committee papers.* Figure 7: Acceptability curve - cetuximab in oral cavity patients ***Figure 7 was presented, but is not replicated here. See committee papers.***	
Merck	**2.7 Shortcomings of trial based model** **2.7.1 Lack of discounting** The trial based model does not incorporate discounting of costs and effects. We do not consider this to be a considerable limitation given the short horizon (5 years). To explore the potential impact of this, we refer the Committee to the scenario analysis described in Section 2.8 below.	See section 4.21 of the FAD.
Merck	**2.8 Scenario analysis** Merck conducted a scenario analysis in which we utilise extrapolation of survival using Weibull curves. In Appendix B, we describe the full methods and results from this analysis. The parametric model has the same structure as the trial based one; a three-state partitioned-survival model in which the mean progression-free survival is estimated as the area under the projected progression-free curve. Mean post-progression survival is estimated as the 'difference' between mean overall survival (the area under the projected OS curve) and PFS. The inputs into this model are conceptually the same as in the trial based model with the following differences: • In this model annual discounting was applied (3.5% costs and benefits) • Full PSA was implemented In the scenario analysis, the deterministic ICER under the assumption of 100% weekly dosing is £[redacted]/QALY and the probabilistic ICER is £[redacted]/QALY. When we apply a weighted average of the real world dosing assumptions, i.e. the result which better reflects the real world cost-effectiveness of cetuximab as a treatment for patients with oral cavity tumours of the head and neck, the ICER is £[redacted]/QALY.	Comment noted. The ERG was unable to validate the probabilistic sensitivity analysis because Merck did not provided an executable model. However, it considered that the probabilistic ICERs were similar to the ICERs estimated in the trial-based model.

Consultee	Comment [sic]	Response
	In summary, two robust analyses confirm that cetuximab is a cost-effective treatment option for patients with tumours of the oral cavity. The ICERs are well below the cost-effectiveness threshold for an end-of-life medicine and the Committee can be reassured that they are not making a decision at the margins of cost-effectiveness. *Appendix A and B were presented, but are not replicated here. See committee papers.*	

Comments received from clinical experts and patient experts

None

Comments received from commentators

None

Comments received from members of the public

None

Summary of comments received from members of the public

None

Single Technology Appraisal (STA): Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck

Merck's response to the Appraisal Consultation Document (received 25th October 2016)

Executive Summary

Merck welcomes the opportunity for ongoing discussions about cetuximab in combination with platinum-based chemotherapy for a subgroup of patients with recurrent/metastatic cancer of the head/neck. Cetuximab is the standard of care for patients with this diagnosis who have no treatment alternatives beyond chemotherapy and oral cavity patients are recognised as a group with a particularly high unmet need.

Cetuximab's efficacy in patients with oral cavity tumours was confirmed in a pre-defined subgroup analysis in the EXTREME trial. There is a strong biological rationale for the greater efficacy seen in this group than in the overall population. Oral tumours over-express EGFR and it follows that an EGFR inhibitor would therefore have more activity. Related to its chimeric structure, cetuximab also has an immunotherapeutic action. Together these mechanisms contribute to cetuximab's efficacy in both the pre and post progression state. The trend towards greater efficacy in this subgroup is validated by results of panitimumab's SPECTRUM trial and is confirmed in our analysis of 5 year data. Collectively this evidence confirms that the subgroup findings are *unlikely* to be an artefact and on that basis, the treatment meets end of life criteria in patients with tumours in the oral cavity.

For the assessment of cost-effectiveness, we:

- incorporate the five year survival data and a more complete assessment of the oral cavity subgroup
- utilise a trial-based model in the base case given the maturity of the survival data in the EXTREME trial
- revise the price of cetuximab, increasing the level of the simple discount from [redacted] to [redacted].

The results of the trial-based model, incorporating the revised discount, confirm that cetuximab is a cost-effective treatment when added to platinum-based chemotherapy. The ICER, under a weekly dosing assumption, being [redacted]/QALY. In clinical practice, cetuximab is more commonly delivered less frequently (every two or three weeks). As per the NICE methods guide, it is appropriate for the Committee to take into account real life use of the drug in their deliberations and cetuximab's dose has been discussed in depth in the mCRC appraisal running in parallel in which the Committee are accounting for real world costs. In this economic model, the ICER reduces considerably to [redacted]/QALY when accounting for how cetuximab is actually used in the NHS. Overall, the Committee can be confident that they are not being asked to make a judgement at the margins cost-effectiveness. Cetuximab offers value for money to the NHS as a treatment for patients with a severe, debilitating tumour with no alternative therapies beyond chemotherapy.

1. Clinical effectiveness

1.1. Clinical validity of oral cavity subgroup

The Committee acknowledged the high unmet need of patients with RM-SCCHN with tumours in the oral cavity. This was on the basis of expert clinical opinion and the evidence that was provided in our resubmission in May 2016, discussed during the first meeting in September 2016. This patient group have a poorer prognosis than patients with tumours in other locations and, in common with the whole population, no alternative treatment options apart from platinum-based chemotherapy.

The Committee, however, have some concerns about the validity of the data in the oral cavity subgroup (from the EXTREME trial) which we discuss in the following section.

1.2. Validity of the results (from the EXTREME trial) in the oral cavity subgroup

Single Technology Appraisal (STA): Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck

We recognise the Committee's concern about the efficacy results that are derived from this small population (n=88) and we hope the following justifications will reassure the Committee of its legitimacy:

- **The subgroup analyses were pre-defined and are confirmed by long-term follow up data**

  The hazard ratio for death in the previous analysis (where median follow-up was 19.1 months in the cetuximab group and 18.2 months in the chemotherapy-alone group) was 0.42 (95% CI 0.26 to 0.67) and in the analysis at the five-year follow up was [redacted].

- **There is a strong biological plausibility for the additional benefit observed in the oral cavity subgroup**

  High epidermal growth factor receptor (EGFR) levels are found in the majority of H&N cancers, it has been specifically evaluated in oral cavity SCCHN. EGFR overexpression has been demonstrated in oral cavity tumours and, in turn, this has been shown to correlate with, and predict poor prognosis for these patients in a number of studies (Sheu, 2009; Laimer, 2007; Storkel, 1993; Thomas, 2012).

- **Comparable results are seen with panitumumab (another EGFRi) in oral cavity patients with a low probability that this is due to chance**

  Panitumumab has been studied in both locally advanced and recurrent/metastatic head and neck cancer too. The panitumumab trial – SPECTRUM (Vermorken, 2013) – shows a similar trend in magnified benefit in patients with tumours of the oral cavity to that observed in the EXTREME study with cetuximab, see Figure 1 and Figure 2. PFS was significantly improved in the patient subgroup in both the EXTREME and SPECTRUM trials, with better HRs in each compared with the results seen in the ITT populations [ITT EXTREME (PFS HR: 0.54, 95% CI 0.43 – 0.67) and ITT SPECTRUM study (PFS HR: 0.78, 95% CI 0.66 – 0.92)].

  A similar trend holds with overall survival with a significant improvement in OS in the oral cavity subgroup in EXTREME, confirmed (albeit not significant) by the SPECTRUM study. In both cases, the HRs are improved compared with the results seen in the respective overall populations in each trial [ITT EXTREME (OS HR: 0.80, 95% CI 0.64 –

0.99) and ITT SPECTRUM study (OS HR 0·87, 95% CI 0.73 – 1.04)]. This evidence demonstrates the differential sensitivity to EGFR inhibition in a tumour where EGFR expression is amplified and confirms that the improved outcomes for patients with oral tumours is clinically driven, rather than being a chance finding.

Cetuximab has immunotherapeutic properties too and, as a chimeric (part mouse, part human) IgG1 antibody, has been shown to activate antibody dependent cellular cytotoxicity (ADCC). It activates the immune system to recruit natural killer cells which have the ability to lyse tumour cells (Rivera, 2008). The dual mechanism of action of cetuximab may contribute to the efficacy of cetuximab both in the pre- and post-progression state and a resultant improvement in overall survival and may help explain the observed differences in outcomes between cetuximab and panitimumab as outlined in the rational above.

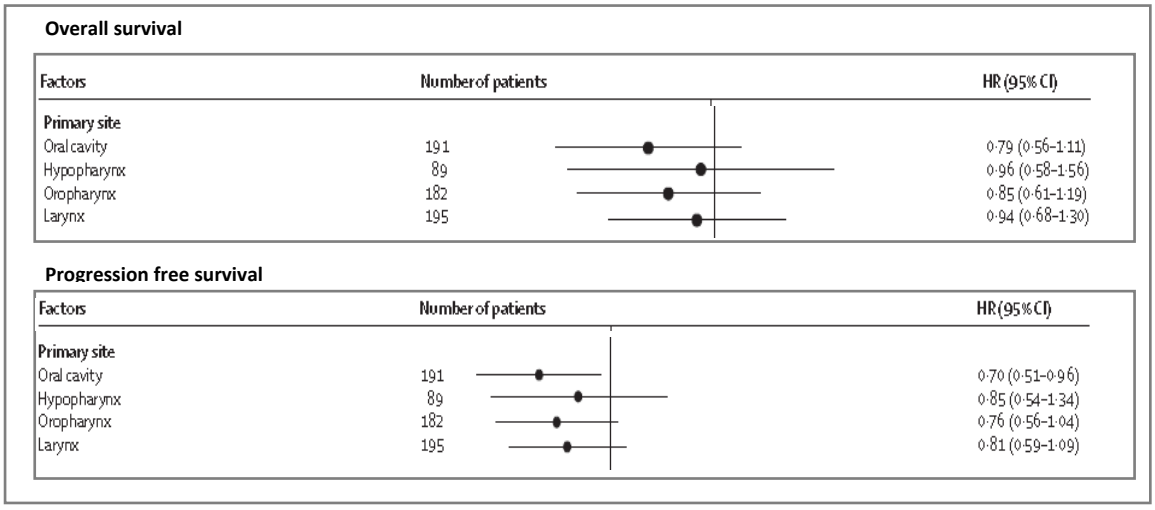

Figure 1: Subgroup analyses from the SPECTRUM study (Vermorken, 2013)

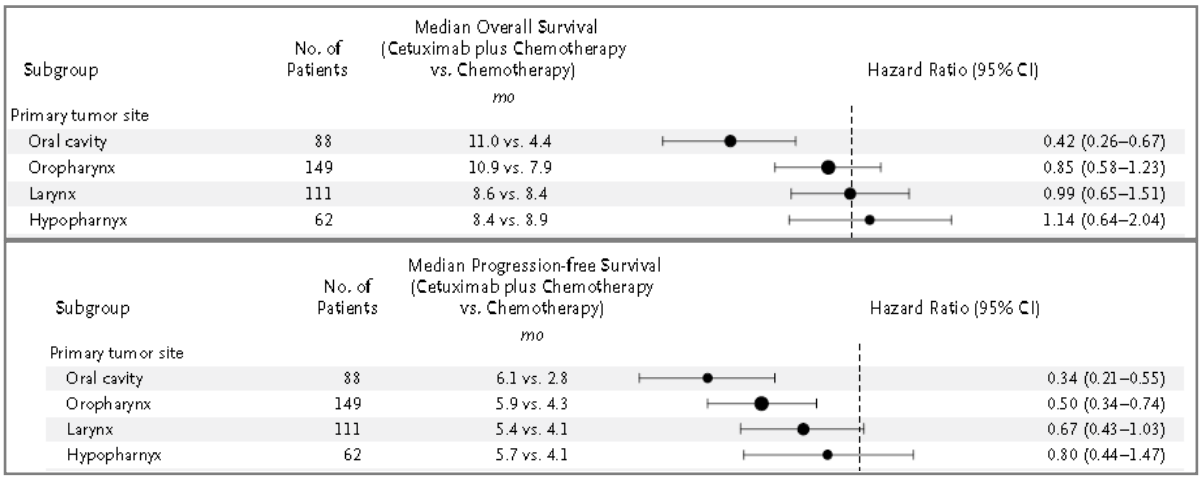

Figure 2: Subgroup analyses form the EXTREME study (Vermorken, 2008)

1.3. The place of cetuximab in the treatment of head and neck cancer patients

The 'EXTREME' regimen is considered standard of care in international guidelines such as those produced by NCCN and ESMO (NCCN 2016, Gregoire 2010, Parikh 2016). In the recent update to the NCCN guidelines cetuximab with platinum-based chemotherapy (EXTREME regimen) remains the only category 1 recommendation for patients with first line RM SCCHN (NCCN guidelines 2016). Moreover, in a recent review of treatment options for RM SCCHN in the Journal of Clinical Oncology 2015 they stated that "The only regimen to demonstrate survival superiority is platinum, 5 FU and cetuximab" (Sacco, 2015).

As a result, several ongoing phase III immune-oncology trials in 1st line RM SCCHN (patients who are untreated for recurrence and/or metastasis) utilise cetuximab plus platinum-based chemotherapy as the comparator, confirming its place as the established standard of care across the world. These are:

- CHECKMATE 651 - Phase III trial in 490pts – nivolumab plus ipilumumab versus EXTREME (NCT02741570)
- KEYNOTE 048 – Phase III trial in 825pts – pembrolizumab plus platinum plus 5FU versus pembrolizumab versus EXTREME (NCT02358031)
- KESTREL – Phase III trial in 760pts – durvalumab plus tremelimumab verus durvalumab versus EXTREME (NCT02741570)

Single Technology Appraisal (STA): Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck

In oral cavity RM SCCHN, a specific subset of the disease with a particularly poor outcome, the benefit of cetuximab relative to platinum-based chemo is magnified, providing patients with 6 months of extra survival. Based on a protocol-defined subgroup analysis, the Committee can be confident that the results represent the effect of cetuximab in this patient population. We urge the panel to approve cetuximab in this setting, so that patients with limited treatment alternatives and poor prognosis can continue to receive benefit from this treatment.

In summary:

- Patients with tumours of the oral cavity have a high unmet need as these tumours tend to be larger and cause significant burden to patients who have a worse prognosis in terms of survival and quality of life.

- There is a clear biological rationale as to why EGFR inhibitors would have a greater effect on oral cavity tumours as these have a reported increase in EGFR receptors therefore would be expected to be more sensitive to EGFR inhibition.

- The subgroup analyses of 2 phase III trials of EGFR inhibitors showed a clear OS and PFS benefit in this patient subgroup in pre-planned analyses, and the oral cavity subgroup derived the most benefit of all subgroups in both trials.

2. Health Economics

Summary of Health Economics section

In brief, five-year survival data for the oral cavity subgroup of the EXTREME trial are very mature; only two patients are censored in the PFS analysis and three in the OS analysis. Therefore, we present a trial-based analysis as the base case assessment of the cost-effectiveness of cetuximab. This immediately removes any uncertainty associated with extrapolation which, as we show in a scenario analysis, is somewhat arbitrary.

In our base case model, the cost inputs are derived as follows:

- Costs of treatment are a product of the average total number of whole vials delivered to patients in the EXTREME trial and the unit cost of a vial; by using actual trial data we avoid the need to retrospectively apply a correction to predicted doses when the model doesn't match the actual trial doses (i.e. a 'dose-intensity' correction)
- Treatment-related costs (i.e. resource use associated with administration) are a product of the average number of *dosage* sessions per treatment per patient and the cost per session (itself a product of the resource use and cost)
- Costs of adverse events are estimated as a product of the 'interventions' associated with adverse events and the unit cost of each 'intervention'
- Non treatment-related health state costs are estimated as in the previous model by applying a weekly PFS and PPS cost for time spent in each of those health states.

Efficacy (QALYs) over the five year horizon is estimated as the product of time in progression free and time in post-progression and the utilities associated with each state.

When real world dosing patterns are accounted for in the economic model, cetuximab is a cost-effective treatment option for patients with tumours of the oral cavity versus chemotherapy alone. The ICER in this analysis is [redacted]/QALY. When 100% weekly dosing is assumed, the ICER is [redacted]/QALY.

In a scenario analysis in which an extrapolation based model is used, the deterministic ICER assuming 100% weekly dosing is [redacted]. The PSA analysis aligns with this giving an ICER of [redacted]/QALY.

When real world dosing patterns are accounted for, the ICER falls to [redacted]/QALY.

In summary, two robust analyses confirm that cetuximab is a cost-effective treatment option for patients with tumours of the oral cavity. The ICERs are well below the cost-effectiveness threshold for an end-of-life medicine and the Committee can be reassured that they are not making a decision at the margins of cost-effectiveness.

2.1. Revised base case analysis

In preparation for this resubmission, Merck have spent considerable time debating the appropriate approach to the economic model. We had previously intended to update the existing Excel-based economic model with the latest survival data from the EXTREME trial, update the extrapolations and tailor the model to the oral cavity subgroup as much as possible. Upon further analysis we have determined that, in the context of the latest data from the EXTREME study, extrapolation of the survival data is unnecessary and introduces complexity and uncertainty. We are therefore presenting a trial based analysis as the base case to address the decision problem in this re-appraisal. We are not submitting this as an Excel model, but instead walk the ERG through its inputs in the remainder of the document.

The primary rationale for this approach is the maturity of the survival dataset at five-year follow up in patients with tumours of the oral cavity. The tables below demonstrate this.

Table 1: Progression free survival at five years in oral cavity subgroup in EXTREME trial

Oral cavity patients	Cetuximab + chemotherapy (n=46)	Chemotherapy (n=42)
Censored	1	1
Progression or dead	45	41

Table 2: Overall survival at five years in oral cavity subgroup in EXTREME trial

Oral cavity patients	Cetuximab + chemotherapy (n=46)	Chemotherapy (n=42)
Censored	1	2
Died	45	40

In our opinion, a trial-based model is the least controversial analysis given that it does not involve extrapolation and instead will censor those patients who are alive/progression-free at the end of the five-year period. The approach is likely to be conservative as, while it censors both benefits and costs from the assessment, the impact of censoring QALY gains will outweigh the impact of censoring costs as the censored patients at 5 years are likely to be long-term survivors.

We conduct an extrapolation based model as a scenario analysis – as described in Section 2.8, however the selection of parametric curve fits for the data is arbitrary and we feel unable to justify projected survival gains on the basis of three surviving patients for all extrapolations except Weibull, which best fit the KM PFS and OS data to five years.

2.2. Model structure

Conceptually, the model structure remains the same.

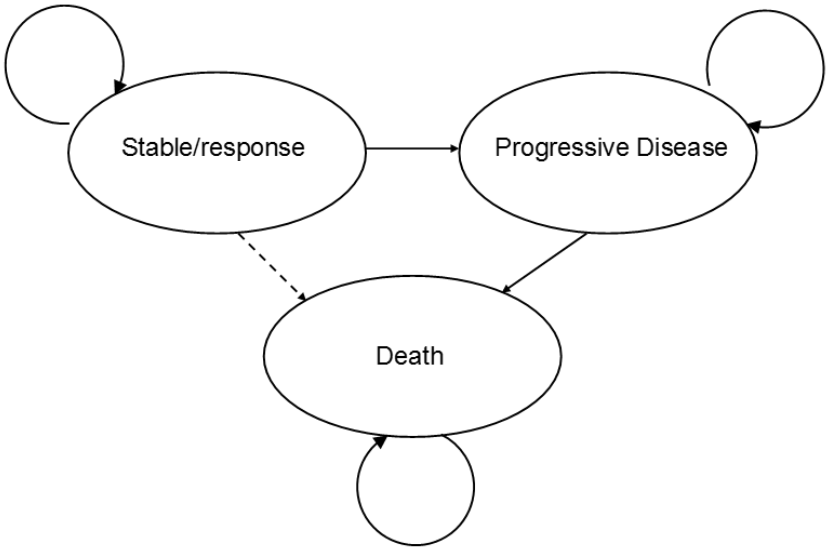

Figure 3: Conceptual model structure

The key model characteristics are:

- Total progression-free time is derived directly from the individual patient data (IPD) as a simple per patient average of the total time spent in PFS using five year survival data from EXTREME. Average time in the post-progression survival (PPS) state is estimated by subtracting this from the mean per patient overall survival.
- Patients receive cetuximab with cisplatin/carboplatin + (5-FU) or cisplatin/carboplatin + (5-FU) only when in the stable/response health state. Patients with 'progressive disease' receive palliative care, a mixture of various chemotherapy, surgery and radiation therapy as observed in the oral cavity subgroup in the EXTREME trial.
- Comparator therapy is platinum-based chemotherapy regimens (5-Flurouracil combined with cisplatin)
- NHS and PSS perspective
- Five-year time horizon

- Resource use and drug costs were updated in April to reflect the latest costs available using 2014/2015 NHS reference costs (NHS, 2014/15) for inpatient, outpatient and investigations; Personal Social Services Research Unit (PSSRU) 2015 for primary care costs and eMIT (June 2015) (eMIT, 2015) and BNF 71 (BNF, 2016) for drug costs. The cost of neutropenia was adjusted from 2012/13 to 2015 assuming 3.7% inflation for transfusions (OHE, 2012).

2.3. Cost of cetuximab

Merck have revised the discount on cetuximab's list price from [redacted] to [redacted]. The level of the discount remains commercial in confidence. We have received confirmation from the Department of Health that they are content with the revision and that this can be considered as part of the ongoing appraisals for cetuximab (this one and the ongoing mCRC MTA).

2.4. Inputs into the trial based model

There are three sets of inputs for both treatment arms that we require for the calculation of cost-effectiveness in the trial-based model:

- Mean survival (progression-free and overall)
- Total costs (treatment cost, administration cost, cost of adverse events, non-treatment related state costs)
- Pre- and post-progression utilities

We will not be presenting an Excel-based model for the trial based assessment. Instead, in the following sections we will set out clearly and transparently how these three sets of inputs have been estimated for cetuximab+chemotherapy and for chemotherapy alone.

2.4.1. Mean survival

We analysed the five-year data in the oral cavity subgroup of the EXTREME trial, estimating the restricted mean progression-free and overall- survival at five years. The results are presented below in Figure 4, Figure 5 and Table 3.

Consistent with the earlier data cut, progression free survival at five-year follow up was significantly improved in the cetuximab arm versus chemotherapy for patients with tumours of the oral cavity [redacted]. The same trend was seen with overall survival [redacted].

[redacted]

[redacted]

The restricted mean survival times (days / years) in each arm is presented in Table 3.

Table 3: Restricted mean survival (days) at five-years

oral cavity patients	cetuximab	chemo	Δ
progression free survival	[redacted]	[redacted]	[redacted]
overall survival	[redacted]	[redacted]	[redacted]
post progression survival	[redacted]	[redacted]	[redacted]

In summary, the survival inputs for the estimate of cost-effectiveness in this decision problem are:

PFS: Cetuximab = [redacted] days | chemotherapy = [redacted] days

OS: Cetuximab = [redacted] days | chemotherapy = [redacted] days

2.4.2. Total costs

Costs in the analysis fall into one of four categories:

- Treatment costs
- Treatment related costs, e.g. administration
- Costs of treating adverse events
- Non-treatment related health state costs

2.4.2.1. Treatment costs

Lifetime treatment costs of cetuximab and chemotherapy comprise drug and administration costs. In the trial based model, the actual total number of whole vials delivered to patients in the EXTREME trial were estimated in order to avoid the requirement to implement a dose-intensity correction (this was controversial in the previous submission). Using the IPD, we quantified the total number of whole vials per treatment utilised by patients. Results show in Table 4 suggest the average patient used the following vials of treatment during the EXTREME trial.

Table 4: Total vials delivered to oral cavity patients in the EXTREME trial

Treatment arm	Drug	Mean	Minimum	2.50%	Median	97.50%	Maximum
Cetuximab arm	Cetuximab	[redacted]	1	34	50	261	815
	Carboplatin	[redacted]	0	0	4	12	12
	Cisplatin	[redacted]	0	0	0	6	10
	5FU	[redacted]	0	6	10	12	20
Chemotherapy arm	Cetuximab	[redacted]	0	0	0	0	0
	Carboplatin	[redacted]	0	0	1	7	9

	Cisplatin	[redacted]	0	0	0	6	6
	5FU	[redacted]	0	2	5	12	12

The average patient used [redacted] vials of cetuximab which can then be used to estimate the cost of cetuximab. The cost of cetuximab in the model is critical and we can validate the results of this approach with another. The cumulative dose of each treatment per patient in the EXTREME trial is represented in Table 5 below and the number of dosage sessions in Table 6.

Table 5: Cumulative dose of each treatment received per arm in oral cavity subgroup patients at 5 years follow up

	Drug	mean	minimum	2.50%	median	97.50%	maximum
Cetuximab	Cetuximab	[redacted]	88	2,857	4,184	21,840	67,982
	Carboplatin	[redacted]	0	25	394	607	613
	Cisplatin	[redacted]	0	0	0	1,856	2,848
	5FU	[redacted]	0	12,029	17,553	24,507	39,523
Chemo	Cetuximab	[redacted]	0	0	0	0	0
	Carboplatin	[redacted]	0	0	100	546	592
	Cisplatin	[redacted]	0	0	0	1,996	2,334
	5FU	[redacted]	0	4,015	9,554	24,294	24,962

Table 6: Total number of 'dosage' sessions in the EXTREME trial for oral cavity subgroup patients at five year follow up

	Drug	mean	minimum	2.50%	median	97.50%	maximum
Cetuximab	Cetuximab	[redacted]	1.0	11.0	16.0	86.8	271.0
	Carboplatin	[redacted]	0.0	0.3	4.0	6.0	6.0
	Cisplatin	[redacted]	0.0	0.0	0.0	6.0	10.0
	5FU	[redacted]	0.0	3.0	5.0	6.0	10.0
Chemo	Cetuximab	[redacted]	0.0	0.0	0.0	0.0	0.0

	Carboplatin	[redacted]	0.0	0.0	1.0	6.0	6.0
	Cisplatin	[redacted]	0.0	0.0	0.0	6.0	6.0
	5FU	[redacted]	0.0	1.0	2.5	6.0	6.0

From these tables we can estimate the mean dose delivered per 'visit'. For cetuximab this is [redacted] / [redacted] dosages = [redacted] / dose, which – when accounting for wastage – is 3 cetuximab vials (100mg each). On the basis of 3 vials per dose, the total number of vials in [redacted] dosages is [redacted].

In general, a method such as the one we use here which relies on the trial data to reflect dose reductions and dose interruptions is the most accurate reflection of how the drug will be used in clinical practice. The alternative way to estimate total dose of cetuximab is to approximate the expected dose based on posology and apply a dose intensity/exposure correction (which itself is based on the ratio of expected (based on posology): actual (trial dose)). This is the approach that was taken in the previous submission, where a correction was applied to adjust the predicted proportion of patients receiving cetuximab at full dose versus the proportion of patients receiving full dose in the trial. We deem it more accurate to utilise the actual trial data (especially when long term data are available) rather than applying a correction in hindsight when the model doesn't match what the trial observed.

Unit costs of the treatments in each arm are presented in Table 7.

Table 7: Unit costs of cetuximab and chemotherapy vials

Treatment	Costs per vial	Source	Assumption
Cetuximab	[redacted]		
Carboplatin	£33.93	eMIT (June 2015)	EXTREME: dose of AUC 5, for a male, 60 years, 70kg, 170 cm, serum creatine 0,595 mg/dl, use of Chatelut formula , at each cycle
Cisplatin	£12.53	eMIT (June 2015)	EXTREME: 100 mg/m2 for each cycle; BSA chosen of 1.75m2
5-FU	£9.83	eMIT (June 2015)	EXTREME: 1000 mg/m2/day during 4 days at each cycle

Mean treatment costs on the basis of the actual vials and cost per vial are therefore as follows.

Table 8: Cost of treatments in cetuximab arm of EXTREME trial

Cetuximab arm oral cavity patients						
	minimum	25%	median	mean	75%	max

cetuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin	£0	£8	£136	£160	£238	£407
cisplatin	£0	£0	£0	£14	£0	£125
5FU	£0	£59	£98	£87	£118	£197
				Total	[redacted]	

Table 9: Cost of treatments in chemotherapy arm of EXTREME trial

Chemotherapy arm oral cavity patients						
	minimum	25%	median	mean	75%	max
cetuximab	£0	£0	£0	£0	£0	£0
carboplatin	£0	£0	£34	£75	£127	£305
cisplatin	£0	£0	£0	£16	£25	£75
5FU	£0	£20	£49	£58	£79	£118
				Total	**£149**	

2.4.2.2. Treatment-related resource use costs

Treatment related resource use costs are estimated by quantifying the number of 'visits' in the EXTREME trial data for oral cavity patients receiving each of the treatments as laid out in Table 10 below.

Table 10: Number of visits in oral cavity patients in the EXTREME trial

	Total number of visits for oral cavity patients		**Average number of visits *per oral cavity patient***	
Treatment	**Cetuximab (n=46)**	**Chemo (n=42)**	**Cetuximab**	**Chemo**
Cetuximab	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + 5FU	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Carboplatin +5FU	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Cisplatin + 5FU	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Carboplatin + Cisplatin +5FU	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
5FU	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + 5FU	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin + 5FU	[redacted]	[redacted]	[redacted]	[redacted]

The visits are then costed under the assumptions ratified in the previous economic model and sourced from Hopper et al, 2004, i.e. that a visit to receive chemotherapy containing 5FU consists of 4 days inpatient stay on a medical oncology ward and that a visit to receive cetuximab, cisplatin or carboplatin alone consists of an outpatient visit. These assumptions were described in the original submission and are not amended as they are not a subject of critique.

Table 11: Resource use per visit (source: Hopper et al, 2004)

Treatment	Inpatient stay in medical oncology ward per cycle [average days per cycle]	Outpatient drug administration visit [number per cycle]
Cetuximab + Carboplatin + 5-FU	4.0	2.0
Cetuximab + Cisplatin + 5-FU	4.0	2.0
Cetuximab	0.0	3.0
Carboplatin + 5-FU	4.0	0.0
Cisplatin + 5-FU	4.0	0.0
5-FU	4.0	0.0
Carboplatin	0.0	1.0
Cisplatin	0.0	1.0

Inpatient stay in medical oncology ward per day is costed at £362, based on 2014/15 NHS reference costs for day case and regular Day/Night, SB15Z: Deliver subsequent elements of a chemotherapy cycle. The total cost for four days stay is therefore £1448.

An outpatient drug administration visit is costed at £204, based on 2014/15 NHS reference costs for Chemotherapy, SB15Z: Deliver subsequent elements of a chemotherapy cycle.

On the basis of these costs, total lifetime administration costs for patients receiving cetuximab and those receiving chemotherapy are £11,407 and £4,275 respectively. The detail of this estimate is shown in Table 12.

Table 12: Estimating administration costs in trial-based model

Treatment	Average number of visits *per patient*		Unit costs of visit	Total cetuximab administration costs	Total chemotherapy administration costs
	Cetuximab	Chemo			
Cetuximab	[redacted]	[redacted]	£204	[redacted]	[redacted]
Cetuximab + Carboplatin	[redacted]	[redacted]	£204	[redacted]	[redacted]
Cetuximab + Cisplatin	[redacted]	[redacted]	£204	[redacted]	[redacted]
Cetuximab + 5FU	[redacted]	[redacted]	£1,448	[redacted]	[redacted]
Cetuximab + Carboplatin +5FU	[redacted]	[redacted]	£1,448	[redacted]	[redacted]
Cetuximab + Cisplatin + 5FU	[redacted]	[redacted]	£1,448	[redacted]	[redacted]
Cetuximab + Carboplatin + Cisplatin +5FU	[redacted]	[redacted]	£1,448	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	£204	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	£204	[redacted]	[redacted]
5FU	[redacted]	[redacted]	£1,448	[redacted]	[redacted]
Carboplatin + 5FU	[redacted]	[redacted]	£1,448	[redacted]	[redacted]
Cisplatin + 5FU	[redacted]	[redacted]	£1,448	[redacted]	[redacted]
Total treatment-related resource use costs				**£11,407**	**£4,275**

The implicit assumption when generalising the findings from use of this method to the NHS perspective is that cetuximab is administered weekly (i.e. as in the EXTREME trial). As Merck described in the resubmission in May 2016, cetuximab is more commonly administered on a different schedule. Data collected from the UK health care setting showed that while some patients are given cetuximab weekly (45%) over 50% of patients receive cetuximab as either a fortnightly infusion (22%) or once every three weeks, in line with chemotherapy (33%) (Data on File: Instar, June 2015). As such, these projections of administration costs are likely to be **over-estimates** of real world administration costs and consequently the projected ICERs in the trial based model are conservative. We approximate that the administration costs are overestimated by 30% (£11,407 versus £8,060[*]) based on a weighted average of the administration costs in a scenario where the market research assumption is used).

2.4.2.3. Costs of adverse events

In the patient-level EXTREME trial database, the treatment of adverse events is captured as one of several 'interventions':

- None
- Chemotherapy discontinued

[*] Estimated on the basis of a weighted average (as per market research on real world dosing) of total treatment related costs by revising Table 12 for fortnightly and three weekly dosing assumptions.

- Chemotherapy dose reduction
- Chemotherapy delayed
- Concomitant meds given
- New or prolonged hospitalisation
- Procedural surgery

We have quantified how many of these events were applied to patients in the oral cavity subgroup in EXTREME over the five year follow up. Discontinuations and times of initiating concomitant medications are not counted if they are on the same day as another discontinuation or prescription. Hospitalisations are not counted if they are within two days of another hospitalisation.

Table 13: Total interventions in response to adverse events in oral cavity subgroup of EXTREME trial

Intervention in relation to AE	Oral cavity patients	
	Cetuximab	Chemo only
'None'	311	88
discontinuation	68	23
concomitant med	294	140
hospitalization	23	24
surgery	9	9

Table 14: Number of interventions per patient in response to adverse events in oral cavity subgroup of EXTREME trial

Intervention in relation to AE	Oral cavity patients	
	Cetuximab	Chemo only
'None'	6.76	2.10
discontinuation	1.48	0.55
concomitant med	6.39	3.33
hospitalization	0.50	0.57
surgery	0.20	0.21

Table 15: Unit costs of interventions associated with experience of adverse event

Unit costs of reactions	Costs	Source / reference
1 = 'NONE'	£44	PSSRU 2015 pg 177 Per patient contact lasting 11.7 minutes (including carbon emissions (6 KgCO2e)2 (including direct care staff costs, with qualification cost)
10 = 'CHEMOTHERAPY DISCONTINUED'	£158	2014/15 NHS Reference Costs for Outpatient Attendances , 370 Medical oncologist (attendance without treatment)
11 = 'CHEMOTHERAPY DOSE REDUCTION'	£158	2014/15 NHS Reference Costs for Outpatient Attendances , 370 Medical oncologist (attendance without treatment)
3 = 'CONCOMITANT MEDS GIVEN'	£88	Assumed to be equivalent to two GP consultations
4 = 'NEW OR PROLONGED HOSPITALISATION'	£1,810	Assumed 5 days of 2014/15 NHS reference costs for Daycase and regular Day/Night, SB15Z: Deliver subsequent elements of a chemotherapy cycle
5 = 'PROCEDURAL SURGERY'	£3,860	Assumed equal to R2014/15 NHS Reference Costs for Elective Inpatients, weighted average of CA83A and CA83B by casemix volume PLUS 4 days inpatient stay
9 = 'CHEMOTHERAPY DELAY'	£158	2014/15 NHS Reference Costs for Outpatient Attendances , 370 Medical oncologist (attendance without treatment)

Total costs of adverse events can therefore be estimated given the inputs above. This is reflected in Table 16.

Table 16: Total costs of treating adverse events in patients with oral cavity tumours

	Cetuximab	Chemo only	Δ
none	£297	£92	£205
discontinuation	£234	£87	£147
concomitant med	£562	£293	£269
hospitalisation	£905	£1,034	-£129
surgery	£755	£827	-£72
TOTAL	**£2,754**	**£2,333**	£420

2.4.2.4. Non-treatment related health state costs

The final category of costs contributing to the estimate of cost-effectiveness are treatment-independent costs within each health state. Given that many of these costs may be unobserved/unmeasured in the clinical trial itself, we defer to the expert clinical advice given in the previous submission to derive them. These costs were not subject to criticism by the ERG and were updated in May 2016 for the original CDF resubmission as follows.

Table 17: Resource use and cost by health state (independent of treatment) every 3 weeks

	Stable / Response	Progressive	Unit cost	Source
Consultant oncologist	0.3	3.0	£158/consultation	2014/15 NHS Reference Costs for Outpatient Attendances , 370 Medical oncologist (attendance without treatment)
Nurse visits [hours per cycle]	0.0	0.0	£50/hour	PSSRU 2015 pg 178
GP	0.0	0.0	£44 (per consultation of 11.7 minutes)	PSSRU 2015 pg 177 Per patient contact lasting 11.7 minutes (including carbon emissions (6 KgCO2e)2 (including direct care staff costs, with qualification cost
CT-scan	0.5	0.0	£88.05/procedure	2014/15 NHS Reference Costs for Diagnostic Imaging CT Scan of one area - weighted average of RD20A, RD21A and RD22Z by casemix volume
MRI	0.15	0.0	£137.37/procedure	2014/15 NHS reference costs for Diagnostic Imaging, weighted average of RD01A, RD02A and RD03Z by casemix volume
Cost per three weeks	£112.03	£474.00		
Cost per week	£37.34	£158		

To estimate the treatment unrelated costs in each health state in the trial, we applied these weekly state costs to the time in each health state (as described in Table 3). Treatment unrelated costs per treatment arm are therefore as follows.

	Time (weeks [days]) in progression free state	Total treatment unrelated costs in progression free	Time (weeks [days]) in post-progression health state	Total treatment unrelated costs in post-progression	Sum of progression free and post-progression costs
Cetuximab	38.23	£1,428	21.86	£3,454	£4,881
Chemotherapy	18.86	£704	11.43	£1,806	£2,510

Total treatment cost have been estimated for both cetuximab treated and chemotherapy treated patients above. The costs are summarised as follows:

Cetuximab:

- Treatment cost: [redacted]

- Treatment related costs: £11,407
- Adverse events: £2,754
- Treatment unrelated health state costs: £4,881

Chemotherapy:

- Treatment cost: £149
- Treatment related costs: £4,275
- Adverse events: £2,333
- Treatment unrelated health state costs: £2,510

In summary, the cost inputs for the estimate of cost-effectiveness in this decision problem are:

Cetuximab = [redacted]

Chemotherapy = £9,267

2.4.3. Utilities

Utilities for this updated model were derived using the same method as developed for the original submission (NB: the mapping to utilities was not an area of critique and has therefore not been modified). To obtain utility estimates for the PFS and PPS health states, QLQ-C30 scores from the oral cavity subgroup patients only in the EXTREME trial were mapped onto the EQ-5D scores using an algorithm previously developed by Kind et al 2005.

EQ-5D = 0.633 + 0.047*Q29 - 0.124*Q3 -0.167*Q5 -0.086*Q11 -0.102*Q20 -0.082*Q26

The QLQ-C30 scores for the stable/responsive state and progressive/disease state were calculated from the oral cavity data in the EXTREME trial and the utility scores were calculated using the above regression equation. This method is the same as that used in the previous submission. It was not previously challenged and has therefore not been revised for this submission.

Treatment specific values are utilised in the stable/responsive health state in order to capture the differences in quality of life during active treatment caused by either benefit from treatment or resulting from the adverse effects of treatment.

Merck believe that the assumption that cetuximab has a positive effect on quality of life is justified by the EXTREME trial evidence in all patients:

1. Data from EXTREME: there was a significant improvement in the global health status/QoL score in the cetuximab arm (p=0.0415). Symptom scores for problems associated with reduced sexuality, social contact, pain, swallowing, speech, sense problems and social eating all improved in the cetuximab arm, showing the QoL benefit resulting from the significant tumour shrinkage activity of cetuximab. The improvements in swallowing and pain reached statistical significance (p=0.0162 and p=0.0027, respectively) (Mesia, 2010).
2. The best overall response rate for the oral cavity subgroup was 46.5% in the EXTREME trial highlighting the efficacy of tumour shrinkage treatment in this group. This response to treatment measured by reduction in tumour size in a population who are associated with bulky tumours in the mouth region will inevitably have a beneficial impact on patients QoL at the pre-progression "stable/ responsive" disease health state.

Additionally a number of UK H&N oncologists consulted by Merck confirmed that treatment with cetuximab does indeed improve patients' QoL. Expert testimony noted that 'better response means less disease related symptoms means clinical benefit and better QoL'. Another consultant noted that the improvement in time to progression of the disease (PFS) can also be used as a proxy for patients' improvement in their quality of life, and in this case this improvement was 3.3 months beyond that of chemotherapy alone. Another consultant stated that there is improvement in patients' quality of life, 'particularly as oral cancer is impacted by eating/chewing etc. prevents wearing of dentures'. Cetuximab significantly reduces the size of tumours in the oral cavity and therefore can be inferred to improve the lives of patients.

The results of the utility mapping exercise are represented fully in the table below:

		#	mean	SE	minimum	2.50%	50%	97.50%	maximum	standard deviation
Baseline	Cetuximab	25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chemotherapy	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression	Cetuximab	33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chemotherapy	19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	Cetuximab	13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chemotherapy	11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 18 below summarises the utility inputs into the estimate of cost-effectiveness for cetuximab.

Table 18: Utility values utilised in the economic model

Health state	Value
Stable/response with cetuximab	[redacted]
Stable/response with standard treatment	[redacted]
Progressive disease	[redacted]

When these QALYs are applied to the mean survival data in the EXTREME trial, as described in Table 3, the total QALYs in each treatment arm can be estimated.

Table 19: QALYs accruing in each health state in each treatment arm

Cetuximab	PFS	PPS	Total QALYs
Time in health state (years)	[redacted]	[redacted]	
Utility	[redacted]	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]

Chemotherapy	PFS	PPS	Total QALYs
Time in health state (years)	[redacted]	[redacted]	
Utility	[redacted]	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]

2.5. Cost-effectiveness of cetuximab

Using the inputs described in Section 2.4.1, Section 2.4.2 and Section 2.4.3, the cost-effectiveness of cetuximab as a treatment for patients with R/M SCCHN tumours of the oral cavity can be estimated.

Table 20: Costs associated with cetuximab treatment in oral cavity patients

oral cavity patients	cetuximab	chemo only	delta	95% confidence interval		p_value
Treatment costs	[redacted]	£149	[redacted]	[redacted]	[redacted]	0.000
Treatment related costs	£11,407	£4,275	£7,132	(£4,186	£10,077)	0.000
Adverse events	£2,754	£2,333	£420	(-£1,004	£1,844)	0.559
Health state costs	£4,881	£2,510	£2,371	(-£258	£4,463)	0.080
TOTAL	[redacted]	£9,267	[redacted]	[redacted]	[redacted]	0.000

Table 21: Efficacy (QALY) gains associated with cetuximab in oral cavity patients

oral cavity patients	cetuximab	chemo only	delta	95% confidence interval		p_value
QALYs (years)	[redacted]	[redacted]	[redacted]			

Therefore the cost-effectiveness of cetuximab versus chemotherapy for patients with recurrent/metastatic oral tumours is [redacted], however this analysis assumes weekly dosing. When real world dosing is accounted for, i.e. a weighted average of weekly, fortnightly or less, as suggested by the market research described in Section 2.4.2.2, treatment related costs for cetuximab fall to [redacted] and consequently the ICER falls to [redacted]. In conclusion, the treatment is cost-effective under the assumptions of an end of life treatment, which we believe to be justified by the trial evidence.

2.6. Sensitivity analysis

A sensitivity analysis was undertaken in the trial-based model. Uncertainties surrounding the cost effectiveness in the trial based analysis are assessed following the approach as introduced by van Hout et al (1994)[†]. In this approach we used the total per patient costs (here the sum of drug costs, cost of associated care, costs of adverse events and the costs of non-treatment-associated care) and the total per patient effects (here QALYs) and estimated the difference between both arms in these parameters. Using the mean differences and the standard errors around the means we modelled these as a result of a bivariate normal distribution taking the covariance between individual cost and effects as an estimate of the correlation between mean costs and mean effects.

Figure 6 shows the results, where the outer ellipse defines the smallest area holding 95% of the probability density, the middle ellipse defines the smallest area holding 50% of the probability density and the inner ellipse and the smallest area with 5% of the probability density. It is noted that this approach only acknowledges the variation in volumes of resource use and the variation in survival (pre and post progression) and disregards the uncertainty surrounding the estimates of unit costs or the uncertainty surrounding the quality of life scores in pre and post progression states.

[†] Van Hout BA, M Al, GS Gordon, FFH Rutten. Costs, effects and C/E-ratio's alongside a clinical trial. Health Economics, 1994, 3, 309-319.

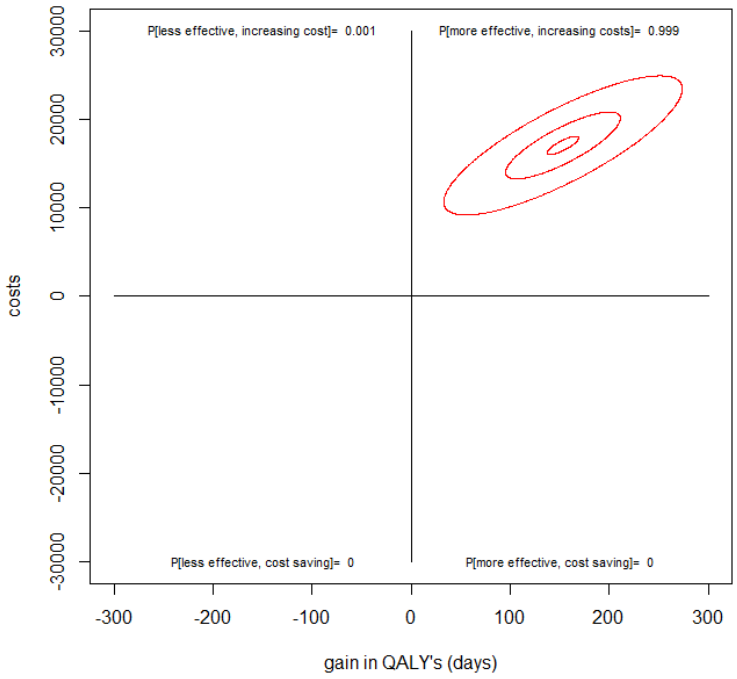

Figure 4: Cost-effectiveness plane - cost-effectiveness of cetuximab in oral cavity patients

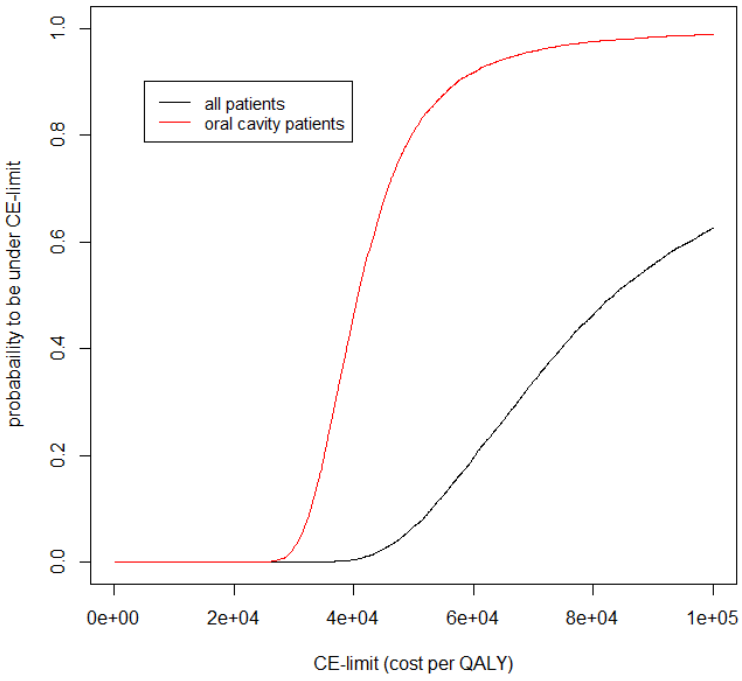

Figure 5: Acceptability curve - cetuximab in oral cavity patients

2.7. Shortcomings of trial based model

2.7.1. Lack of discounting

The trial based model does not incorporate discounting of costs and effects. We do not consider this to be a considerable limitation given the short horizon (5 years). To explore the potential impact of this, we refer the Committee to the scenario analysis described in Section 2.8 below.

2.8. Scenario analysis

Merck conducted a scenario analysis in which we utilise extrapolation of survival using Weibull curves. In Appendix B, we describe the full methods and results from this analysis.

The parametric model has the same structure as the trial based one; a three-state partitioned-survival model in which the mean progression-free survival is estimated as the area under the projected progression-free curve. Mean post-progression survival is estimated as the 'difference' between mean overall survival (the area under the projected OS curve) and PFS.

The inputs into this model are conceptually the same as in the trial based model with the following differences:

- In this model annual discounting was applied (3.5% costs and benefits)
- Full PSA was implemented

In the scenario analysis, the deterministic ICER under the assumption of 100% weekly dosing is [redacted]/QALY and the probabilistic ICER is [redacted]/QALY. When we apply a weighted average of the real world dosing assumptions, i.e. the result which better reflects the real world cost-effectiveness of cetuximab as a treatment for patients with oral cavity tumours of the head and neck, the ICER is [redacted]/QALY.

In summary, two robust analyses confirm that cetuximab is a cost-effective treatment option for patients with tumours of the oral cavity. The ICERs are well below the cost-effectiveness threshold for an end-of-life medicine and the Committee can be reassured that they are not making a decision at the margins of cost-effectiveness.

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Appendix A: Parameter estimates for cross-walk algorithm from QLQ-C30 to EQ-5D utility

	Unstandardized Coefficients	Standard Error
Constant	0.633	.071
Q29 Overall health	0.047	.013
Q3 trouble with short walk	-0.124	.031
Q5 help with dressing washing	-0.167	.047
Q11 trouble sleeping	-0.086	.032
Q20 difficulty concentrating	-0.102	.033
Q26 physical family life impact	-0.082	.031

Source: P Kind. Measuring the value of quality of life in cancer: An index based on EORTC QLQC-30 Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No 16S, 2005: 6013

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Appendix B: Extrapolation based model

Merck has developed an extrapolation based model as a scenario analysis. We submit it as an Excel-based model accompanying this response. It is derived from the model that the ERG will have seen previously, but we have simplified it considerably.

B1: Model structure

The model structure is the same conceptual structure as the trial-based model, see Section 2.2.

In this partitioned-survival model, total progression-free survival time is derived as the area under the extrapolated progression-free survival curve. Time in PPS is derived as the difference between the area under the extrapolated overall survival curve and the progression-free survival curve.

Survival is extrapolated using Weibull curves on the basis of a comprehensive assessment of the projections with a range of alternative parametric extrapolations replicated below. There is less of a difference in the PFS extrapolations, however log-normal and log-logistic extrapolations of OS fit the data best statistically (lowest AIC scores), however the projections of survival gain may be unrealistic. Log logistic for example predicts an 11% increase in the restricted mean survival in cetuximab treatment arm at 5 years versus the actual survival at that point (versus). We determine that the extrapolation using Weibull has the greater face validity, given both the fit to the data and the consistency with the clinical evidence.

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B2: Estimation of treatment costs

Cetuximab: In the extrapolation based model, a linear regression analysis with progression free survival as the dependent variable and number of whole vials as the independent variable was run to assess the relationship between these variables. Figure 9 below presents the results.

In this regression, the constant term of this relationship is interpreted as an estimate of the average number of vials per day. Individual patient's total doses (vials) were rounded up to the nearest 100mg, thereby incorporating wastage in the total dose estimate.

Results show that the mean daily vials used (accounting for wastage) is [redacted] per day. This input is utilised in the extrapolation based model.

[redacted]

Chemotherapy: Chemotherapy costs are estimated following the method used in the previous model, namely determining the quantity of drug to be used per three-week cycle and multiplying this by the unit cost and time in PFS.

Unit costs of the chemotherapies and the cost per cycle for chemotherapies are replicated in xxx below.

Table 22: Drug acquisition costs and surgery and radiation costs

	cost per unit	description of unit	dose [mg]	no. of units / vials	Cost for the 3-week cycle	Source	Remarks
Carboplatin	£33.93	per vial 600 mg; 60 ml, 10 mg/ml	1098.6	2.00	£67.86	eMIT (June 2015)	EXTREME: dose of AUC 5, for a male, 60 years, 70kg, 170 cm, serum creatine 0,595 mg/dl, use of Chatelut formula , at each cycle

Cisplatin	£12.53	per vial 100 mg; 100ml, 1 mg/ml	175	2.00	£25.06	eMIT (June 2015)	EXTREME: 100 mg/m2 for each cycle; BSA chosen of 1.75m2
5-FU	£9.83	per vial 2500 mg; 100 ml, 25 mg/ml	7000	3.00	£29.49	eMIT (June 2015)	EXTREME: 1000 mg/m2/day during 4 days at each cycle
Bleomycin	£15.56	per vial 15 mg/15 units	78.75	6.00	£93.36	BNF71	Rx list: 0.25 to 0.50 units/kg (10 to 20 units/m2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly; BSA assumed of 1.75 m2 (1 unit bleomycin equals 1 mg.)
Docetaxel	£12.39	per vial 80 mg; 2ml, 40 mg/ml	131.25	2.00	£24.78	eMIT (June 2015)	Rx list: 75 mg/m2 as a 1 hour intravenous for each cycle; BSA chosen of 1.75 m2
Methotrexate	£0.49	per tablets 10 mg	200	20.00	£9.72	eMIT (June 2015)	RX list: 25 mg/day orally for 4 to 8 days plus 7-10 days of no treatment (8 days of 25 mg/day assumed)
Paclitaxel	£12.74	per vial 150 mg; 25 ml, 6 mg/ml	236.25	2.00	£25.48	eMIT (June 2015)	Given every 3 weeks, administered intravenously over 24 hours at a dose of 135 mg/m2, BSA =1.75 assumed
Vinorelbine	£22.33	per 50 mg; 5ml,10mg/ml	157.5	4.00	£89.32	eMIT (June 2015)	Rx list: 30 mg/m2 administered weekly. The recommended method of administration is an intravenous injection over 6 to 10 minutes; BSA=1.75 assumed
Radiotherapy	£2,914.00 + £362	>3 and <13 fractions	1	1.00	£3,276	NICE STA report for locally advanced SCCHN	2014/15 NHS Reference Costs for Radiotherapy, SC28Z: Deliver a fraction of interstitial radiotherapy
Surgery	£2,412.00 + £1,448		1	1.00	£3,860	NICE STA report for locally advanced SCCHN	R2014/15 NHS Reference Costs for Elective Inpatients, weighted average of CA83A and CA83B by casemix volume

B3: Costs of adverse events

Adverse events are costed by multiplying the proportion of patients in the previous EXTREME datacut with adverse events in each arm multiplied by the unit cost of each adverse event. These data were unavailable for the oral cavity in time for this resubmission and therefore the

proportion of adverse events is derived from the all-patient group in the EXTREME trial. They are essentially unchanged from the previous submission.

Table 23: Proportion of patients with adverse events in each treatment arm

	Cetuximab + standard treatment arm [%pts]	**Standard treatment arm [%pts]**
Anaemia grade 3	13.2%	20.5%
Anaemia grade 4	1.8%	0.9%
Neutropenia grade 3	20.5%	16.7%
Neutropenia grade 4	4.1%	8.4%
Thrombocytopenia grade 3	11.0%	11.2%
Thrombocytopenia grade 4	0.0%	1.4%
Mucositis/ stomatitis/ dysphagia grade 2	29.2%	23.7%
Mucositis/ stomatitis/ dysphagia grade 3	9.6%	10.2%
Mucositis/ stomatitis/ dysphagia grade 4	0.9%	2.3%
Nausea/ vomiting grade 2	46.6%	41.4%
Nausea/ vomiting grade 3	9.1%	7.0%
Nausea/ vomiting grade 4	0.0%	0.9%
Pyrexia grade 3 or 4	0.0%	0.9%
Acne/ rash grade 3 or 4	7.3%	0.0%

The unit costs of the adverse events are based on the previous submission (i.e. derived from the costs in the cetuximab STA for the treatment of locally advanced squamous cell carcinoma of the head & neck (LA SCCHN), Table 13 cost variables. The costs were updated in May 2016 as reflected in Table 24.

Table 24: Unit costs of adverse events

	Base	**Source**
Anaemia grade 3	£516.12	**2014/15 NHS Reference Costs for Non-Elective Short Stay**Invalid source specified. Weighted average SA04G, SA04H, J, SA04K and SA04L by casemix volume
Anaemia grade 4	£516.12	**2014/15 NHS Reference Costs for Non-Elective Short Stay**Invalid source specified. Weighted average SA04G, SA04H, J, SA04K and SA04L by casemix volume
Neutropenia grade 3	£5,671.50	**2012/13 NHS Reference Costs for Non-Elective Short Stay**Invalid source specified. PA45Z: Febrile Neutropenia with Malignancy inflated by 3.5% to 2014/2015 (OHE, 2012)

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Neutropenia grade 4	£5,671.50	**2012/13 NHS Reference Costs for Non-Elective Short Stay**Invalid source specified. PA45Z: Febrile Neutropenia with Malignancy inflated by 3.5% to 2014/2015 (OHE, 2012)
Thrombocytopenia grade 3	£502.63	**2014/15 NHS Reference Costs for Non-Elective Short Stay.**Invalid source specified. Weighted average of SA12G, SA12H, SA12J, SA12k by casemix volume
Thrombocytopenia grade 4	£502.63	**2014/15 NHS Reference Costs for Non-Elective Short Stay.**Invalid source specified. Weighted average of SA12G, SA12H, SA12J, SA12k by casemix volume
Mucositis/ stomatitis/ dysphagia grade 2	£516.13	**2014/15 NHS Reference Costs for Non-Elective Short Stay** Invalid source specified. CB01F: Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0-4
Mucositis/ stomatitis/ dysphagia grade 3	£736.00	**2014/15 NHS Reference Costs for Non-Elective Short Stay**.**Invalid source specified.** CB01E: Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 5-8
Mucositis/ stomatitis/ dysphagia grade 4	£1,109.00	**2014/15 NHS Reference Costs for Non-Elective Short Stay**.**Invalid source specified.** CB01D: Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 9+
Nausea/ vomiting grade 2	£824.97	**2014/15 NHS Reference Costs for Non-Elective Short Stay**Invalid source specified. FZ13C: Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over
Nausea/ vomiting grade 3	£1,484.40	**2014/15 NHS Reference Costs for Non-Elective Short Stay**Invalid source specified. Weighted average of FZ27F and FZ27G by casemix volume
Nausea/ vomiting grade 4	£2,038.09	**2014/15 NHS Reference Costs for Non-Elective Short Stay.**Invalid source specified. FZ27E: Intermediate Therapeutic General Abdominal Procedures, 19 years and over, with CC Score 3+
Pyrexia grade 3 or 4	£2,661.41	**2014/15 NHS Reference Costs for Non-Elective Short Stay**Invalid source specified. WJ02B: Major Infectious Diseases with Single Intervention
Acne/ rash grade 3 or 4	£36.10	**eMIT and BNF 71** Invalid source specified.Invalid source specified. Zineryt 90ml, minocin 100mg MR and diprosone 0.1% 100g cream

*Costs inflated to 2015 assuming 3.7% medical inflation as per ABPI UK NHS medical bill projection 2012-2015. (OHE, 2012)

On the basis of these two sets of inputs, the total costs of adverse events is £2,285 in the cetuximab treatment arm and £2,310 in the chemotherapy only treatment arm.

We are reassured that our approach to costing AEs in the extrapolation based model is sufficient, for two reasons:

- Comparable proportions of all grade AEs across the all patient and oral cavity patient groups (albeit using the previous data cut); see Table 25. It is reasonable to expect that the same pattern would hold with only grade 3/4 events.

Table 25: Adverse events of any grade and cause occuring in EXTREME trial (only those selected for modelling are shown)

	All patients (ITT) EXTREME trial		Oral cavity subgroup patients	
	Cetuximab arm	Chemotherapy arm	Cetuximab arm	Chemotherapy arm
Anaemia	42.5%	53.0%	45.7%	38.1%
Neutropenia	38.4%	39.1%	34.8%	21.4%
Thrombocytopenia	21.9%	24.2%	19.6%	19.0%
Mucositis/ stomatitis/ dysphagia	47.5%	41.4%	52.2%	33.3%
Nausea/Vomiting	94.0%	84.7%	82.6%	64.3%
Pyrexia	22.4%	13.0%	28.3%	11.9%
Acne/rash	49.8%	1.9%	58.7%	0.0%

- Similar adverse event costs in the trial-based model.

B3: Treatment-related costs

Costs associated with treatment delivery (assuming weekly dosing of cetuximab) are described in Table 26 below.

Table 26: Costs associated with delivery of treatments

Treatments	tx associated costs	Detail (assumptions from Hopper et al, 2004)
Cetuximab + Carboplatin + 5-FU	£1,856	4 days inpatient stay per cycle + 2 outPx drug administration visits
Cetuximab + Cisplatin + 5-FU	£1,856	as above
Cetuximab	£612	3 outpatient drug administration visits
Carboplatin + 5-FU	£1,448	4 days inpatient stay per cycle
Cisplatin + 5-FU	£1,448	4 days inpatient stay per cycle
5-FU	£1,448	4 days inpatient stay per cycle

Bleomycin	£612	3 outpatient drug administration visits
Carboplatin	£204	1 outpatient drug administration visit
Cisplatin	£204	as above
Docetaxel	£204	as above
Gefitinib	£0	
Methotrexate	£204	as above
Paclitaxel	£204	as above
Vinorelbine	£204	as above

B4: Costs unrelated to treatment

These costs are estimated using methodology consistent with the trial-based model and the previous submission. The weekly health-state costs (not related to treatment) have been described previously (Section 2.4.2.2). They are applied to the time spent in progression-free and post-progression health states.

B5: Utilities

Utilities in the model have been updated to reflect the oral cavity subgroup. The method and the resulting utilities are described in detail in Section 2.4.3.

B6: Results

The results of the extrapolation based model assuming 100% weekly dosing are presented in Table 27.

Table 27: Cost-effectiveness results of extrapolation-based cost-effectiveness model

	undiscounted	discounted
Costs	[redacted]	[redacted]
life years	0.56	0.53
QALYs	0.39	0.38
Cost per life year	[redacted]	[redacted]
Cost per QALY	[redacted]	[redacted]

As we have previously described, cetuximab is more commonly delivered on a less than weekly schedule. Data collected from the UK health care setting showed that while some patients are given cetuximab weekly (45%) over 50% of patients receive cetuximab as either a fortnightly infusion (22%) or once every three weeks, in line with chemotherapy (33%) (Data on File: Instar,

June 2015). These real life dosing costs should be accounted for in the economic model otherwise cetuximab is unfairly penalised.

In the economic model which assumes weekly dosing, the cost of administration of cetuximab in combination with chemotherapy and as a monotherapy is outlined in Table 26. These costs were used to estimate the cost-effectiveness results when real world dosing is taken into account, reflected in Table 28.

Table 28: Costs of drug administration per three-week cycle

	Cetuximab in combination with chemotherapy (first 6 cycles)	Cetuximab monotherapy (cycles 7+)
Weekly	£1,856; see Table 26	£612; three outpatient visit
Fortnightly	£1,652; assumes 4 inpatient days and 1 outpatient visit	£408; two outpatient visits
Three weeks	£1,448; assumes 4 inpatient days only	£204; one outpatient visit

The results of the three economic models when these administration costs are assumed are shown Table 29.

Table 29: Results of economic model under different dosing assumptions

	ICER (£/QALY, discounted)	Real world dosing
Weekly	[redacted]	45%
Fortnightly	[redacted]	22%
Three weeks	[redacted]	33%

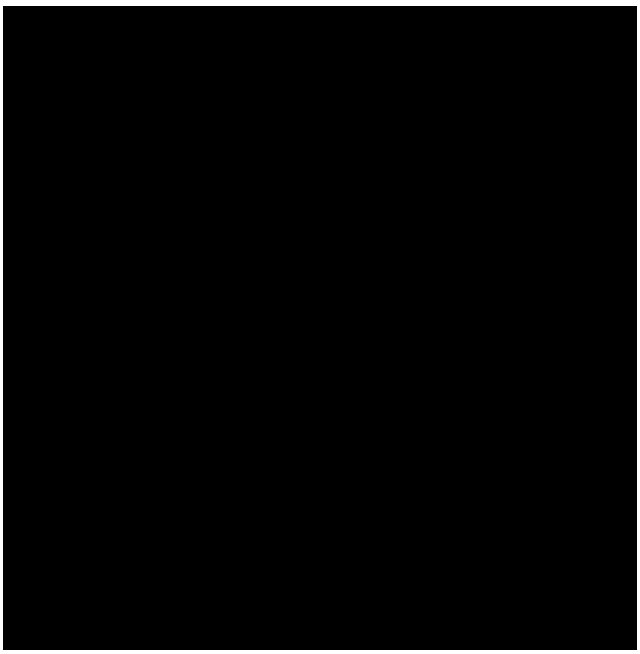
A weighted average of these dosing assumptions, i.e. the result which better reflects the real world cost-effectiveness of cetuximab as a treatment for patients with oral cavity tumours of the head and neck is [redacted] /QALY.

B6: Probabilistic sensitivity analysis

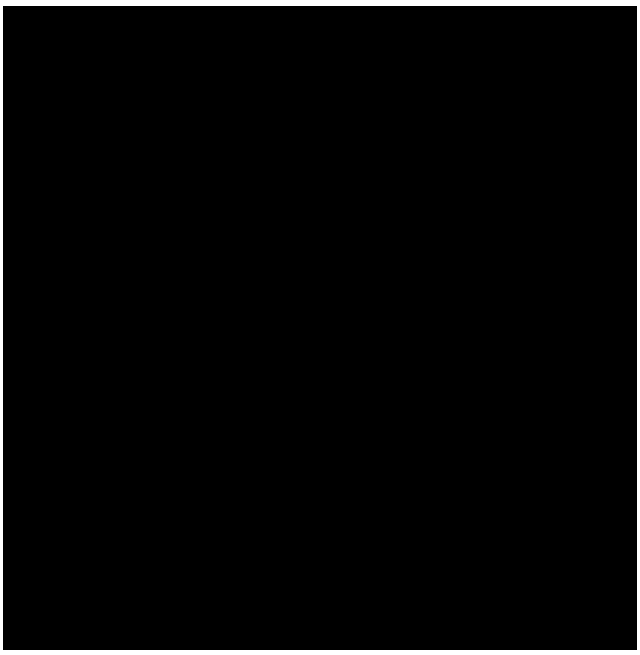
A probabilistic sensitivity analysis was undertaken to test the robustness of the results against the uncertainty around the parameter point estimates. We defined a probability distribution for various model inputs and a value for each input was randomly and simultaneously selected – over 10,000 iterations – from the specific distribution for each model input. The setup of the PSA does not vary from the previous model as this was not a subject of critique by the ERG. Average costs and QALYs were calculated using these random values to determine the probabilistic ICER.

- For treatment related resource use, a gamma distribution was assumed with the confidence intervals defined by a standard deviation of 0.2 times the cost estimate.
- For daily average cetuximab vials, the standard error of the regression coefficient (as described in Appendix B2), i.e. 0.02488 was used and a normal distribution was assumed.
- For utilities, a normal distribution was assumed utilising the standard errors of the state specific utility estimates.
- Uncertainty around adverse events was explored using a beta distribution based on the standard error of the prevalence in the all patient population (see Section B3).
- Non-treatment related costs were varied with a gamma distribution with the confidence intervals defined by a standard deviation of 0.4 times the cost estimate.
- Uncertainty in extrapolation of PFS and OS was explored using the Cholesky decomposition method in which Weibull parameters were assumed to follow a normal distribution and a correlation matrix (as shown in the Excel model) was used to generate correlated random Weilbull parameters for the simulations.

Results of the probabilistic sensitivity analysis are reported below in Figure 10 and Figure 11.



[redacted]



[redacted]

The mean costs and QALY's generated in the PSA are replicated in the table below where the ICER for cetuximab versus chemotherapy in the oral cavity subgroup is [redacted]/QALY (this assumes 100% weekly dosing and is therefore an underestimate of the true cost-effectiveness of cetuximab).

Table 30: Cost-effectiveness of cetuximab for patients with oral cavity tumours

	undiscounted	discounted
Costs	[redacted]	[redacted]
life years	0.57	0.55
QALY's	0.41	0.39
Cost per life year	[redacted]	[redacted]
Cost per QALY	[redacted]	[redacted]

B7: Conclusions

In conclusion, the deterministic and probabilistic ICERs for cetuximab as a treatment for patients with RM SCCHN and tumours of the oral cavity confirm that the treatment is a cost-effective use of NHS resources.

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ERG REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cancer Drugs Fund rapid reconsideration of NICE Guidance TA172

Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck

[ID1016]

ERG consideration of additional evidence submitted by the company in response to the Appraisal Consultation Document (October 2016)

Confidential until published

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UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

The National Institute for Health and Care Excellence (NICE) is in the process of assuming responsibility for the Cancer Drugs Fund (CDF). The CDF provided a mechanism for some cancer treatments which failed to receive a positive recommendation when originally appraised for clinical and cost effectiveness for general use in the NHS, to be provided on a case-by-case basis to selected patients referred to the CDF by their clinician. As part of the transition, a number of historic technology appraisal decisions are being rapidly reconsidered to determine the future status of treatments currently provided only through the CDF, i.e. whether they may now be recommended for general use, continue within the scope of the revised CDF scheme, or not be provided at all through the NHS. The Liverpool Reviews and Implementation Group (LR*i*G) at the University of Liverpool has been commissioned to review the company submission (CS) to assist a NICE Appraisal Committee (AC) in reconsideration of NICE Guidance TA172. The original Single Technology Appraisal (STA) was conducted in 2008-09 and final NICE guidance was issued in June 2009 and did not recommend cetuximab in combination with platinum-based chemotherapy for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck for use in the NHS.

2 CONTEXT AND APPROACH TO RAPID RECONSIDERATION

To allow these rapid reconsideration exercises to proceed with the minimum risk of delay, the normal single technology appraisal (STA) procedures have been restricted in scope for the company in making a resubmission, and for the Evidence Review Group (ERG) tasked with providing an independent assessment of the company submission (CS). It is assumed that the primary clinical effectiveness data will remain essentially unchanged from the original appraisal and therefore no additional clinical evidence will be accepted by NICE. The cost effectiveness analyses included in the CS needs to reflect the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) (ICERs) as identified in the published guidance. It is anticipated that the main areas to be considered by the AC will relate to changes in the costs associated with treatment including any special NHS pricing agreements that have been agreed since the original STA was carried out.

3 SPECIFIC DIFFICULTIES WITH THIS RAPID RECONSIDERATION

The initial CS was considered by the Appraisal Committee on the 29th September 2016, and an Appraisal Consultation Document (ACD) was issued which did not recommend the use of cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck. The company approached NICE seeking permission to submit additional evidence in response to the initial ACD decision, employing revised clinical trial results involving more mature five-year follow-up data from the single clinical trial on which the original appraisal decision was based. NICE agreed to this request, and the company provided a submission document and revised decision model which was received by the ERG on 12th January 2017. Accepting the new submission at this stage has significant consequences for the task faced by the ERG:

- The ERG received the additional submission only 6 working days prior to the deadline for submission of their commentary on the new information in order to meet the timetable for a second AC meeting on the 26th January 2016;

- The ACD response is quite different in form and content from the previous CS, involving a new base case economic result independent of the decision model previously employed decision model;

- A new set of extended clinical trial survival data have been used to parameterize the revised base case, but the detailed Kaplan-Meier survival data which had previously been requested by the ERG for their consideration of the initial CS, has not been provided for the new extended survival data;

- The revised electronic decision model supplied by the company is incompatible with the new non-model base case, as it uses a different basis for representing patient survival - overall survival(OS) and progression-free survival (PFS) – and is only cited by the company as a way of indicating the sort of probabilistic cost-effectiveness results that might be expected with the new data.

In order to provide any useful commentary in time for the second consideration by the AC of this rapid review on 1st February 2017, the ERG has reluctantly concluded that it is necessary to limit its consideration to the new evidence in the following ways:

- Restricting attention to the new base case analysis and the evidence on which it is based, excluding any consideration of the amended electronic model;

- Focusing attention primarily on the new OS and PFS evidence available only in graphical form;

- Checking the accuracy/validity of the other data and parameter values used to generate the new base case economic results;

4 NEW BASE CASE ECONOMIC ANALYSIS

4.1 Elements of the trial-based economic analysis

Three types of information are employed by the company in tabular form to populate their new trial-based base case analysis:

1) Mean PFS and OS;

2) Total costs: treatment costs, treatment administration costs, adverse event costs and other patient costs related to their current health state, but independent of the type of primary treatment to which patients are allocated;

3) Health-state specific patient utility values when patients are progression-free, and following disease progression.

4.2 Survival extrapolation

4.2.1 Progression-free survival

The company stated that they have used five-year follow-up data from oral cavity patients in the EXTREME trial directly to estimate PFS in both trial arms without using any survival modelling, and have estimated the gain in PFS as the arithmetic difference between the Kaplan-Meier PFS estimates in the two trial arms. On this basis, the company claims a PFS advantage for cetuximab+CTX over CTX only of [redacted]. However, there is an imbalance in the trial data available up to five-years in that all oral cavity patients in the CTX only arm have suffered an event except for 1 patient censored early in the trial, but one cetuximab+CTX patient remained event-free after five years follow-up. This patient alone contributed additional estimated PFS benefit to the analysis for more than [redacted] prior to the five year analysis limit. The potential for substantial random error in favour of the cetuximab+CTX arm being introduced on the basis of the timing of a single patient event is considerable, and warrants careful consideration.

Figure 1 PFS data from five-year follow-up of EXTREME clinical trial

The Kaplan-Meier results for the two arms of the EXTREME trial (Figure 1), show a consistent pattern of a steadily increasing separation until only [redacted]% of patients are estimated to be event-free. Thereafter, the trajectory of the PFS curve changes suddenly in both arms to a much shallower trajectory, indicative of a sharp reduction in the underlying hazard rate for disease progression or death. The similarity of the late phase trends in both arms suggests that there may be a common cause for this phenomenon. The ERG therefore explored the effect of incrementally offsetting the CTX only survival curve forward in time to assess whether the apparently similar trends were confirmed when the final phases of the two Kaplan-Meier curves are overlaid. Figure 1 shows the results of the optimal offset of [redacted] months, indicating that the late phase of both Kaplan-Meier curves are virtually identical.

This finding provides a very simple alternative method for estimating the size of the PFS advantage for cetuximab+CTX vs CTX only: we can ignore the section of each survival curve onwards from the time when PFS is [redacted]%, since these segments are identical in size and will therefore not contribute to the net advantage for cetuximab+CTX over CTX only. This means comparing the area under the curve (AUC) for cetuximab+CTX as far as point A to the AUC for CTX only to point B. This yields an estimated mean PFS gain of [redacted], [redacted] less than the mean PFS gain estimated by the company.

The ERG has explored pooling the Kaplan-Meier data from both arms in the common end phase, and found that the data indicate a clear linear trend in cumulative PFS hazard equivalent to a simple constant risk (exponential) long-term trend.

Figure 2: Relative time to progression/death plot for five-year follow-up of EXTREME trial data for oral cavity subgroup

Further insight into the underlying treatment/disease interaction is afforded by the comparison of time-to-event data in Figure 2. This shows clearly that during the early phase of the trial (when PFS falls from 100% to 10%) there is a very strong linear relationship consistent with the effect of cetuximab based therapy being to extend the time spent by patients in PFS by a steady proportion of [redacted]. However this relationship no longer applies for the remaining 10% of surviving patients for whom little or no further PFS benefit is afforded by randomization to treatment with cetuximab.

4.2.2 Overall survival

The pattern of OS survival curves in the five-year follow-up data is similar to that for PFS (cf. Figure 3 with Figure 1), though requiring a smaller time offset ([redacted]) to show equivalence of the long-term data.

The ERG has estimated the mean gain in OS attributable to use of cetuximab to be [redacted], [redacted] less than the company estimated mean difference of [redacted].

Figure 3: Five-year follow-up Kaplan-Meier OS data from the EXTREME trial

4.2.3 Post-progression survival

Post-progression survival (PPS) cannot be analyzed directly for the EXTREME trial without access to detailed clinical trial data. However, the mean PPS survival gain attributable to treatment with cetuximab+CTX can be estimated as the difference between the mean gain in OS and the mean gain in PFS. This indicates that more than a third of the overall survival benefit may arise during the post-progression period. This is uncommon in trials of treatments for advanced cancer with chemotherapy, where more often the disease reverts to following the typical progressive disease trajectory, independent of the choice of prior treatment.

4.2.4 'End of Life' criteria

The mean estimated survival of patients in the oral cavity subgroup who received only conventional chemotherapy within the EXTREME trial is [redacted]. The estimated gain in OS attributable to combining cetuximab with chemotherapy in the EXTREME trial is [redacted]. This analysis suggests that cetuximab+CTX may qualify for consideration under the 'end of life' criteria.

4.3 Costs

4.3.1 Treatment costs

The revised base case analysis presented by the company uses a further reduction in the price of cetuximab in which the unit cost per vial has been changed from £[redacted] to £[redacted].

The company have used the average number of 100mg vials of cetuximab per patient estimated from the EXTREME trial as the basis for estimating the acquisition cost of cetuximab. In addition they use the number of treatment sessions per patient in estimating the cost of administering cetuximab. They estimate the average dose of cetuximab administered per patient session to be 253mg, on which basis they calculate the average cost per treatment assuming three 100mg vials per patient-treatment (including the initial session which requires a higher dose). This approach to estimating drug costs leads to a serious anomaly when compared to the conventional method using the prescribed dose and patient characteristics.

The dosing regimen for cetuximab is 400mg/m^2 for the initial dose, followed by 250mg/m^2 weekly thereafter. Details of the distribution of body surface area (BSA) in the oral cavity subgroup of the EXTREME trial have not been provided by the manufacturer. However, using UK survey results for Head and Neck cancer patients (Sacco et al), and the gender balance in the EXTREME trial, the ERG estimates the mean BSA to be 1.815 m^2.

This allows the calculation of the mean prescribed dose of cetuximab per patient session as 726mg for the initial treatment (400mg/m^2), and 454mg for subsequent weekly treatments (250mg/m^2). This suggests that the initial dose would require seven to eight 100mg vials per patient, and subsequent doses four to five 100mg vials per patient, an increase compared to the company estimate of 150% for the initial dose and 50% for subsequent doses.

Examination of the EXTREME trial report tables reveals the source of this large discrepancy: throughout the trial report statistics on the mean quantity of drugs (other than carboplatin) administered to patients are stated in terms of the mg per m^2, so that this may be directly compared to the protocol planned dosage levels. It appears that those carrying out the estimation of drug costs for this appraisal have mistakenly assumed that the totals reported for 'cumulative dose received' were in fact simple totals of the milligram content of drug administered to all patients. As a result all the estimates of costs for prescribed by BSA were deficient by a multiple of the mean BSA of the patient population.

The company has not provided demographic details relating to the oral cavity subgroup on which to base drug costing calculations. For the overall EXTREME population mean BSA is

given as 1.747 m^2 which only includes a minority of UK patients. Instead the ERG prefer to use the mean BSA (1.815 m^2) for Head and Neck cancer chemotherapy patients in a UK survey, adjusted to match the gender ratio in the EXTREME trial, increasing the cost of drugs other than carboplatin by 81.5% compared to the estimates provided in the company's new base case analysis.

4.3.2 Treatment administration costs

The method of calculating treatment administration costs, based on NHS Reference Costs applicable to each scheduled dose, is applied to data collected in the EXTREME trial. The company argues that in a survey of some UK patients receiving cetuximab, about half were found to be receiving treatment either every 2 weeks or every three weeks. It is not clear how this was managed in terms of the total dose administered per cycle, the extent of sub-optimal dosing or the impact of these different regimens on treatment outcomes. For consistency, the ERG considers that it is not appropriate to model the patient survival outcomes reported in the EXTREME trial whilst also reducing treatment administration costs; this fails to consider the potential impact on efficacy of variations in treatment intensity and dose timing. Since EXTREME is the only source of evidence relevant to the small subgroup being considered, the ERG believes that there is too much uncertainty attached to this deviation from the trial evidence to warrant the proposed amendment to the cost-effectiveness analysis.

4.3.3 Adverse event costs

The method used to apply cost estimates to the adverse event data from the EXTREME trial is clearly set out in Tables 13-16 of the company's response to the ACD. The ERG has no comment to make on the method used, and the net difference in cost between the treatments as relatively minor and unlikely to influence the estimated ICER significantly.

4.3.4 Other health state costs

The ERG does not dispute the method used for estimating the costs associated with patient health states unrelated directly to the treatment received. However, the calculations depend on the survival estimation methods described above. When these are taken into account the estimated cost per patient in PFS increases for both treatments, but at different rates so that the incremental cost per patient for this category of cost falls by £161.

4.4 Health state patient utility

The company have rightly pooled the utility mapped EXTREME quality of life data in relation to patients in the post-progression state, on the grounds that there is no statistically

significant difference between the estimates obtained for the different treatments. Applying the same logic to the larger number of observations available for patients prior to progression yields a net mean difference of 0.048 with a 95% confidence interval of -0.046 to +0.143. There is therefore no statistical justification for not also using a common pooled estimate for the pre-progression health state.

It is also worth observing that there are only 52 observations in total (33 from an unknown number of cetuximab patients and 11 from an unknown number of chemotherapy patients). Knowledge of whether a patient is randomized to receive the interventional treatment, as in this trial, is known to influence patient responses to quality of life questions. In addition there is evidence that patients with a good response to treatment are more likely to participate in completing repeated quality of life questionnaires. In summary, the data available from the EXTREME trial represents a very weak basis for inferring reliable differential utility effects between competing treatments. The ERG therefore maintains its view that a pooled PFS utility value of 0.683 should be applied to both treatment arms. This has the effect of increasing the company's new base case ICER by £[redacted] per QALY gained.

4.5 Discounting

The company has not applied standard discounting to their revised base case on the grounds that "We do not consider this to be a considerable limitation given the short horizon (5 years)." The ERG has applied discounting of both costs and outcomes to the results of the revised base case analysis and found that this change alone increases the estimated ICER by £[redacted] per QALY gained, and therefore should certainly be taken into account.

5 RESULTS

Table 1 summarises the cost effectiveness results obtained using the revised base case analysis submitted by the company, alongside results using the ERG amended analysis including the ERG revised OS and PFS estimates using the five-year follow-up results from the EXTREME trial. The four issues raised by the ERG each generate important increases in the estimated ICER for the use of cetuximab in combination with chemotherapy compared with chemotherapy alone. The overall effect of these changes is to increase the ICER in excess of £50,000 per QALY gained.

Table 2 Revised cost and outcome effects of ERG model amendments relative to the company's revised base case analysis

Model Scenario	Cetuximab + CTX costs	Cetuximab + CTX QALYs	CTX only costs	CTX only QALYs	Incremental costs	Incremental QALYs	Estimated ICER (£/QALY)	ICER change
Company revised base case	**£[redacted]**	**0.759**	**£[redacted]**	**0.361**	**£[redacted]**	**0.398**	**£[redacted]**	**-**
ERG survival analysis (PFS/PPS/OS)	£[redacted]	0.742	£[redacted]	0.376	£[redacted]	0.366	£[redacted]	£[redacted]
ERG drug costing	£[redacted]	0.759	£[redacted]	0.361	£[redacted]	0.398	£[redacted]	£[redacted]
Common PFS utility value	£[redacted]	0.743	£[redacted]	0.374	£[redacted]	0.369	£[redacted]	£[redacted]
Applying discounting	£[redacted]	0.730	£[redacted]	0.369	£[redacted]	0.361	£[redacted]	£[redacted]
ERG revised base case	**£[redacted]**	**0.717**	**£[redacted]**	**0.378**	**£[redacted]**	**0.339**	**£[redacted]**	**£[redacted]**

6 REFERENCES

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