NICE National Institute for Health and Care Excellence

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CDF Rapid Reconsideration

Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck (review of TA172) [ID1016]

Contents:

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

NICE National Institute for Health and Care Excellence

Cetuximab for treating recurrent and/or metastatic head and neck cancer

Rapid reconsideration of TA172

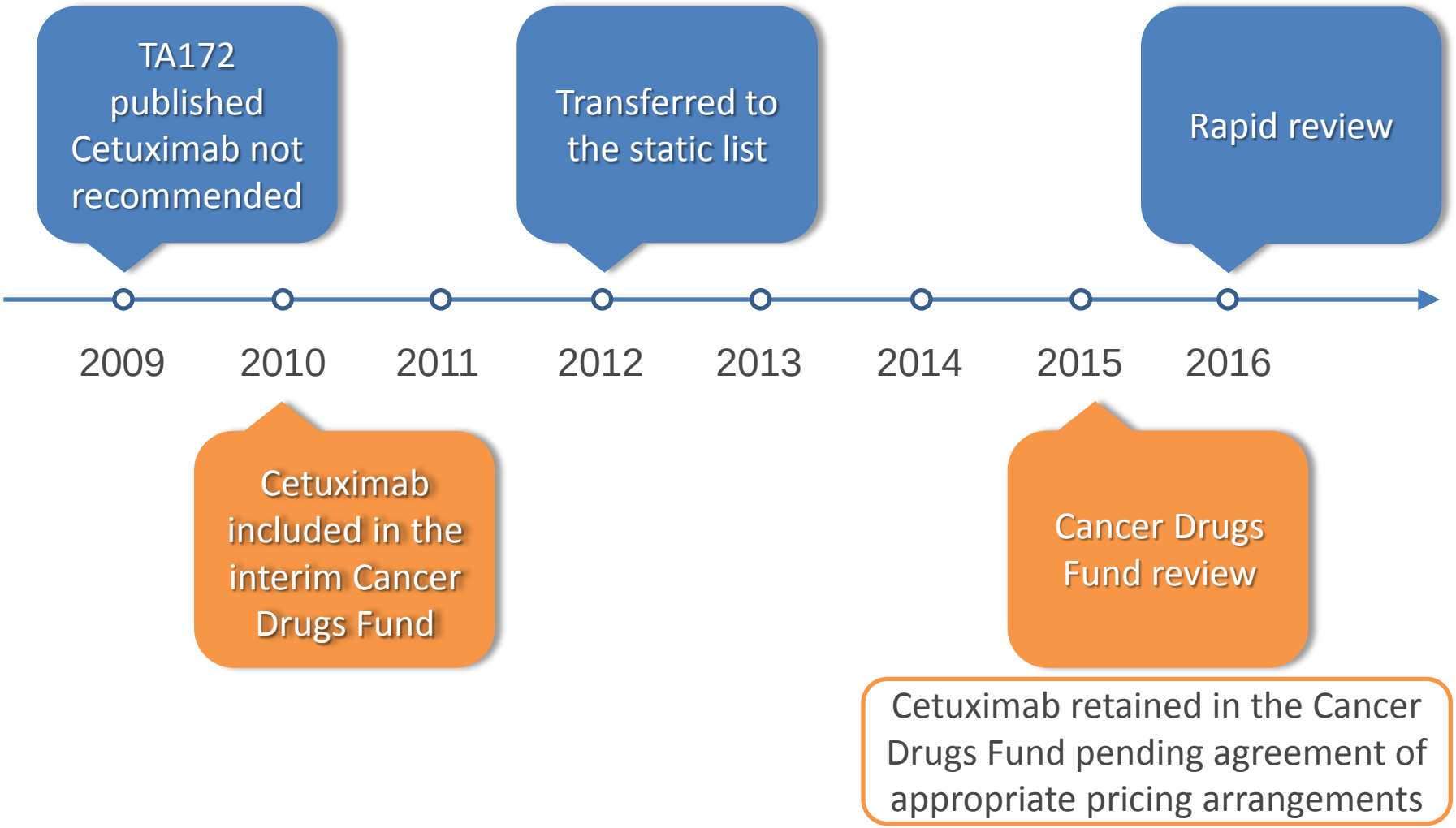
Public observer slides

29th September 2016

Cetuximab

Mechanism of action	Chimeric monoclonal antibody to epidermal growth factor receptor - Inhibits cell proliferation and stimulates antibody-dependent cellular cytotoxicity
Marketing authorisation	'Treatment of patients with squamous cell cancer of the head and neck (SSCHN) in combination with platinum-based chemotherapy for recurrent and/or metastatic disease'
Dose	Initial dose of 400 mg/m^2 with subsequent weekly doses of 250 mg/m^2 i.v. administration

Cetuximab for recurrent and/or metastatic SCCHN – history



Company's original decision problem (TA172)

Population	Adults with metastatic and/or recurrent squamous cell carcinoma of the head and neck for whom platinum-based chemotherapy is appropriate
Intervention	Cetuximab plus platinum-based chemotherapy
Comparators	Platinum-based chemotherapy Cisplatin combined with fluorouracil is the standard of care in the UK
Outcomes	Overall survival, progression-free survival, tumour response, adverse events, health-related quality of life
Economic analyses	Cost per life years and incremental cost per quality-adjusted life years Lifetime time horizon Costs considered from an NHS and Personal Social Services perspective
Special considerations	Subgroups defined by performance status, previous treatments and response to previous treatments

Comparator and evidence

Adults with metastatic and/or recurrent squamous cell carcinoma of the head and neck for whom platinum-based chemotherapy is appropriate

Cetuximab + Cisplatin (or carboplatin) plus fluorouracil

Cisplatin (or carboplatin) plus fluorouracil

EXTREME Open-label, multicentre RCT

No systemic chemotherapy in the previous 6 months

Cetuximab + cisplatin or carboplatin plus fluorouracil

Cisplatin or carboplatin plus fluorouracil

1° Overall survival
2° Progression-free survival, best overall response, disease control, time to treatment failure, response duration, quality of life

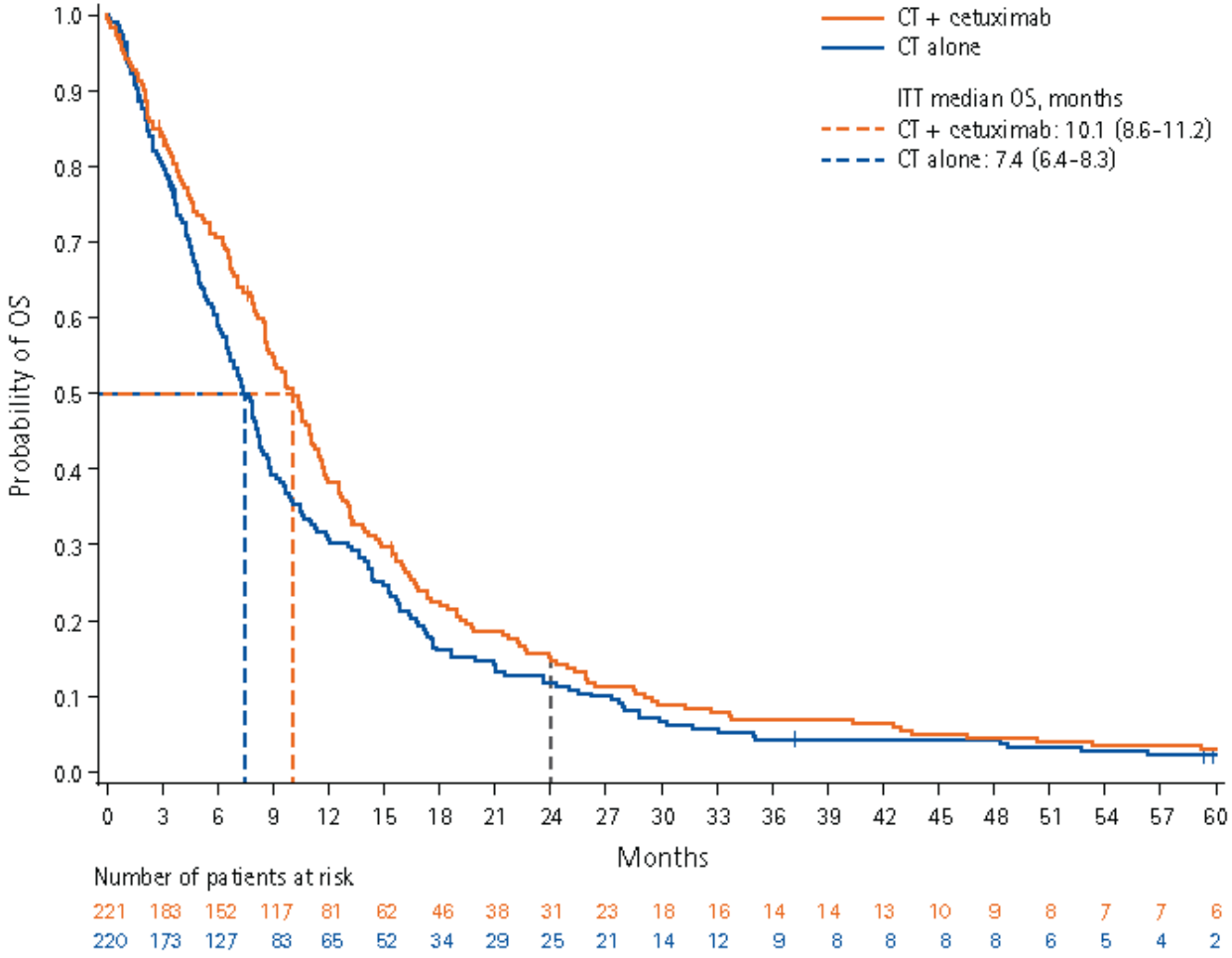
TA172 EXTREME results ITT population (n=442)

Treatment outcome	Cetuximab + chemotherapy* (n=222)	Chemotherapy* only (n=220)	Analysis (95% CI)	p value
Median overall survival (months)	10.1	7.4	HR 0.80 (0.64 to 0.99)	0.004
Median progression-free survival (months)	5.6	3.3	HR 0.54 (0.43 to 0.67)	<0.001
Median overall response rate (%)	36	20	OR 2.33 (1.50 to 3.60)	<0.001
Median disease control** (%)	81	60	OR 2.88 (1.87 to 4.44)	<0.001

*Chemotherapy=cisplatin or carboplatin plus fluorouracil
**Includes complete response, partial response and stable disease

Source: Table 1, page 11 of the company submission

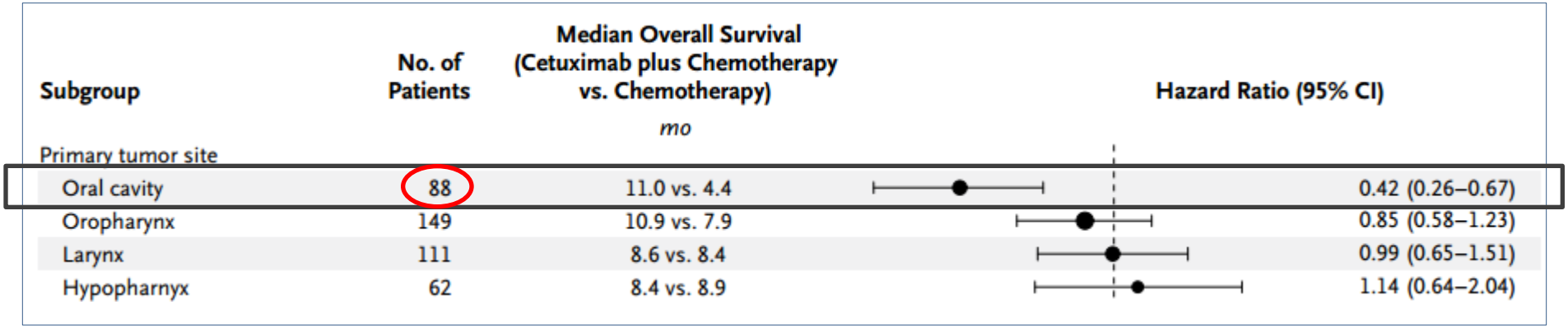
TA172 EXTREME trial
Overall survival - ITT population



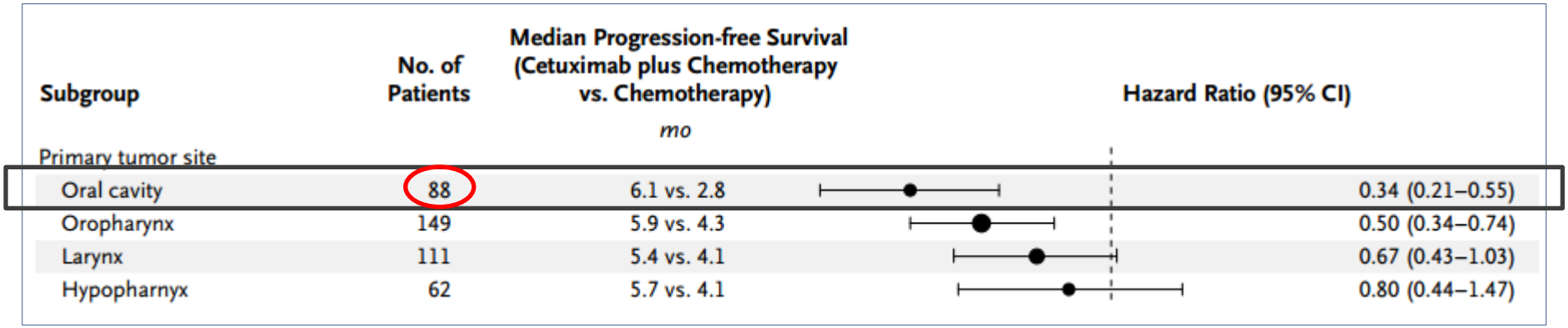
CT, chemotherapy; ITT, intention-to-treat; OS, overall survival.

Source: Figure 5, page 39 of the company submission; Vermorken et al. (2014) ASCO annual meeting

TA172 EXTREME subgroup analysis – primary tumour site



Subgroup	No. of Patients	Median Overall Survival (Cetuximab plus Chemotherapy vs. Chemotherapy) *mo*	Hazard Ratio (95% CI)
Primary tumor site			
Oral cavity	88	11.0 vs. 4.4	0.42 (0.26–0.67)
Oropharynx	149	10.9 vs. 7.9	0.85 (0.58–1.23)
Larynx	111	8.6 vs. 8.4	0.99 (0.65–1.51)
Hypopharnyx	62	8.4 vs. 8.9	1.14 (0.64–2.04)



Subgroup	No. of Patients	Median Progression-free Survival (Cetuximab plus Chemotherapy vs. Chemotherapy) *mo*	Hazard Ratio (95% CI)
Primary tumor site			
Oral cavity	88	6.1 vs. 2.8	0.34 (0.21–0.55)
Oropharynx	149	5.9 vs. 4.3	0.50 (0.34–0.74)
Larynx	111	5.4 vs. 4.1	0.67 (0.43–1.03)
Hypopharnyx	62	5.7 vs. 4.1	0.80 (0.44–1.47)

Chemotherapy=cisplatin or carboplatin plus fluorouracil

Source: Figure 2, page 14 of the company submission

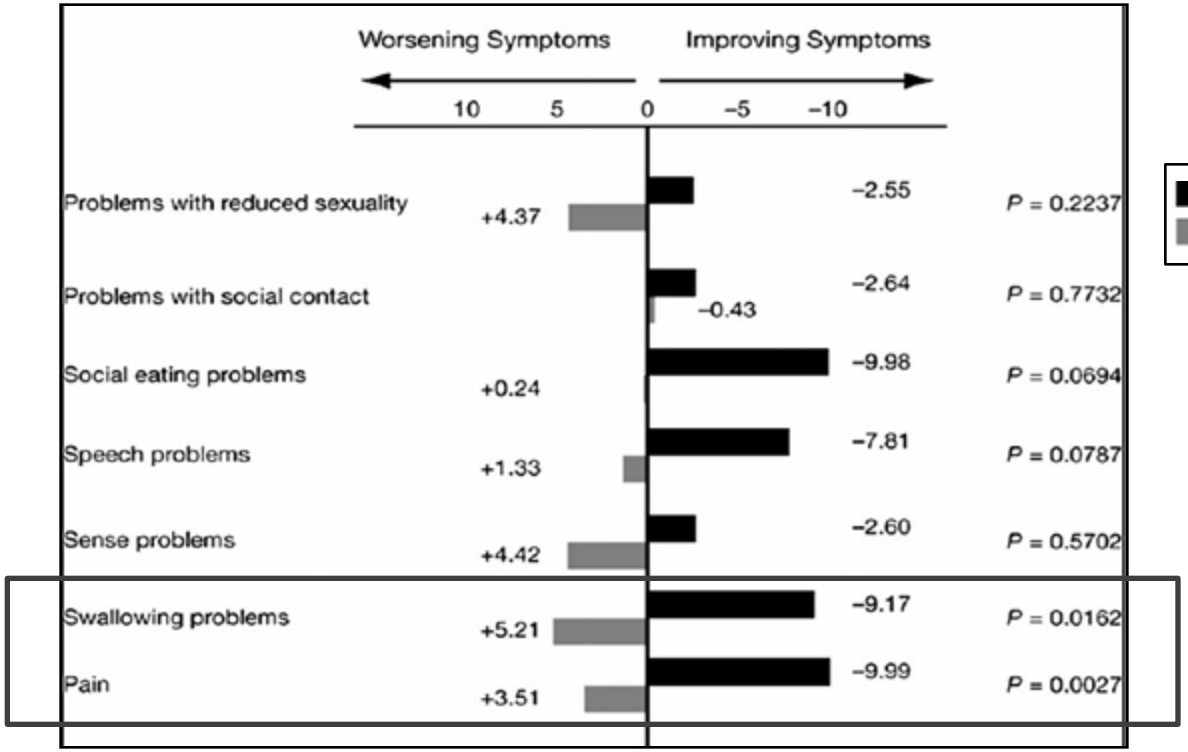
TA172 EXTREME results
Oral cavity subgroup (n=88)

Treatment outcome	Cetuximab + chemotherapy* (n=46)	Chemotherapy* only (n=42)	Analysis (95% CI)
Median overall survival (months)	11.0	4.4	HR 0.42 (0.26 to 0.67)
Median progression-free survival (months)	6.1	2.8	HR 0.34 (0.21 to 0.55)
Best overall response rate (%, 95% CI)	[redacted]	[redacted]	NR
Median disease control rate** (%, 95% CI)	[redacted]	[redacted]	NR

*Chemotherapy=cisplatin or carboplatin plus fluorouracil
**Includes complete response, partial response and stable disease
NR=not reported

Source: Table 2, page 13 of the company submission

TA172 EXTREME symptom scores – ITT population



Overall score
p=0.0415

- Information gathered using EORTC QLQ-H&N35, a tumour specific questionnaire developed for use in patients with head and neck cancer
- Specific results are not available for the oral cavity cancer subgroup

Source: Table 4, page 18 of the company submission

Committee's preferred assumptions and company responses (1)

Preferred assumption	Company response
Calculate dose using a higher BSA from UK audit of general head and neck cancer patients, weighted for the gender balance in the EXTREME trial	Not accepted. Audit patient group not large enough to generalise, recurrent/metastatic phase of oral cavity cancer linked to weight loss, ratio of men to women in EXTREME may overestimate likely average BSA
Use the same utility in each treatment in each health state	Not accepted. Cetuximab has a good response rate which influences QoL in the oral cavity cancer subgroup

Committee's preferred assumptions and company responses (2)

Preferred assumption	Company response
Replace the projection modelling of costs and outcomes used in the base case with a comparison of costs and outcomes at 24 months (end of follow-up period in the EXTREME trial)	Not accepted. Outcomes from the 5 year follow up of EXTREME are more favourable for the ITT population than the model. Assume also applies to oral cavity subgroup
Include a mid-cycle correction on the base case results	Correction accepted but half-cycle not mid-cycle correction implemented
Use the most recent and consistent price base	Accepted. Updated unit costs included

Company submission – Scope

- The scope of TA172 included adults with metastatic and/or recurrent squamous cell carcinoma of the head and neck
- This submission focusses on first line treatment of the oral cavity cancer subgroup with ‘extremely high unmet need’
  - Early stages associated with limited pain and symptoms
  - High risk of recurrence
  - Static survival rates which are lower than other head and neck cancers
  - ‘Clinical evidence suggests cetuximab is effective across the whole population’ but ‘modelling indicates a low likelihood of cost-effectiveness’ driven by large administration costs
  - Another anti-EGFR (panitumumab) showed a significant increase in progression-free survival in patients with oral cavity cancer (n=191) compared to other SSCHNs, however no increase in overall survival was seen across the study compared to chemotherapy alone[1]
- Case for end of life criteria

[1]*Vermorken et al. (2013) Lancet Oncology*

Company submission
Evidence and economic model

- 5-year survival data from the EXTREME trial is available but results are not available for the oral cancer subgroup
- Half-cycle correction
- Updated unit costs
- Revised simple discount patient access scheme agreed with the Department of Health conditional upon positive guidance for cetuximab as a first line treatment for metastatic colorectal cancer

CDF reconsideration
Issues for consideration

- The submission is focussed on the oral cavity subgroup. Does the Committee consider this appropriate given the small subgroup size?
- Are the company's and the ERG's estimates of the ICER plausible?
- Is the dose reconciliation used to correct for the mismatch between the predicted and actual number of vials of cetuximab used appropriate?
- The patient access scheme is subject to positive guidance for cetuximab as a first-line treatment for metastatic colorectal cancer (ongoing MTA review; expected publication date Nov 2016). Taking this proposed scheme into account, can cetuximab be recommended for use in the NHS?

Company's economic model

- Decision problem addressed
  - Cost-effectiveness of cetuximab plus platinum-based chemotherapy compared to standard platinum-based chemotherapy alone
  - First-line treatment of patients with recurrent and/or metastatic SSC of the oral cavity
    - More restrictive than the scope and decision problem in TA172
- Two-arm state transition model
  - Course of disease reflected by 3 mutually exclusive health states (stable/response; progressive; death)
  - Distribution of patients between the health states over time described using Weibull distributions for progression-free survival and overall survival as estimated from the EXTREME trial

Company's new base case using PAS – Oral cavity subgroup

	Cetuximab + chemotherapy*	Chemotherapy* only	Difference
Total costs (£)	[redacted]	£10,889	[redacted]
QALYs gained	0.67	0.32	0.35
ICER (£/QALY)			[redacted]

Base case cost effectiveness results based on EXTREME trial includes a BSA of 1.75 m^2, treatment specific utility, half cycle correction applied to costs and benefits, and 2014/15 costs

Chemotherapy=cisplatin or carboplatin plus fluorouracil

Typographical error in company submission. [redacted] is the correct cost

Source: Table 10, page 44 of the company submission

Company's additional 'scenario analysis'

Variable	ICER (£/QALY)	Difference in ICER (£/QALY)
Base case	[redacted]	
BSA of 1.83 m^2 (versus 1.75 m^2)	[redacted]	[redacted]
Equivalent utility estimates (0.67) across both treatment arms pre-progression (versus treatment specific utilities)	[redacted]	[redacted]
Cetuximab administered in line with UK clinical practice*	[redacted]	[redacted]

*[redacted]

Source: Tables 12-14, page 48-50 of the company submission

End of life criteria
Evidence from EXTREME trial

	ITT population (n=442 total)	Oral cavity cancer subgroup (n=88 total)
Life expectancy normally <24 months	7.4 months (median)	4.4 months (median)
Extension to life normally >3 months	2.7 months (median)	6.6 months (median)
No alternative treatment with comparable benefits available	Currently treated with palliative intent	

- Additional data from a single arm trial of patients (n=54) who received combination treatment and reported median OS of 14 months[1]

Sources: Data derived from Tables 1 and 2 (pages 11 and 13) of the company submission;
[1]Guigay et al., 2015 Annals of Oncology

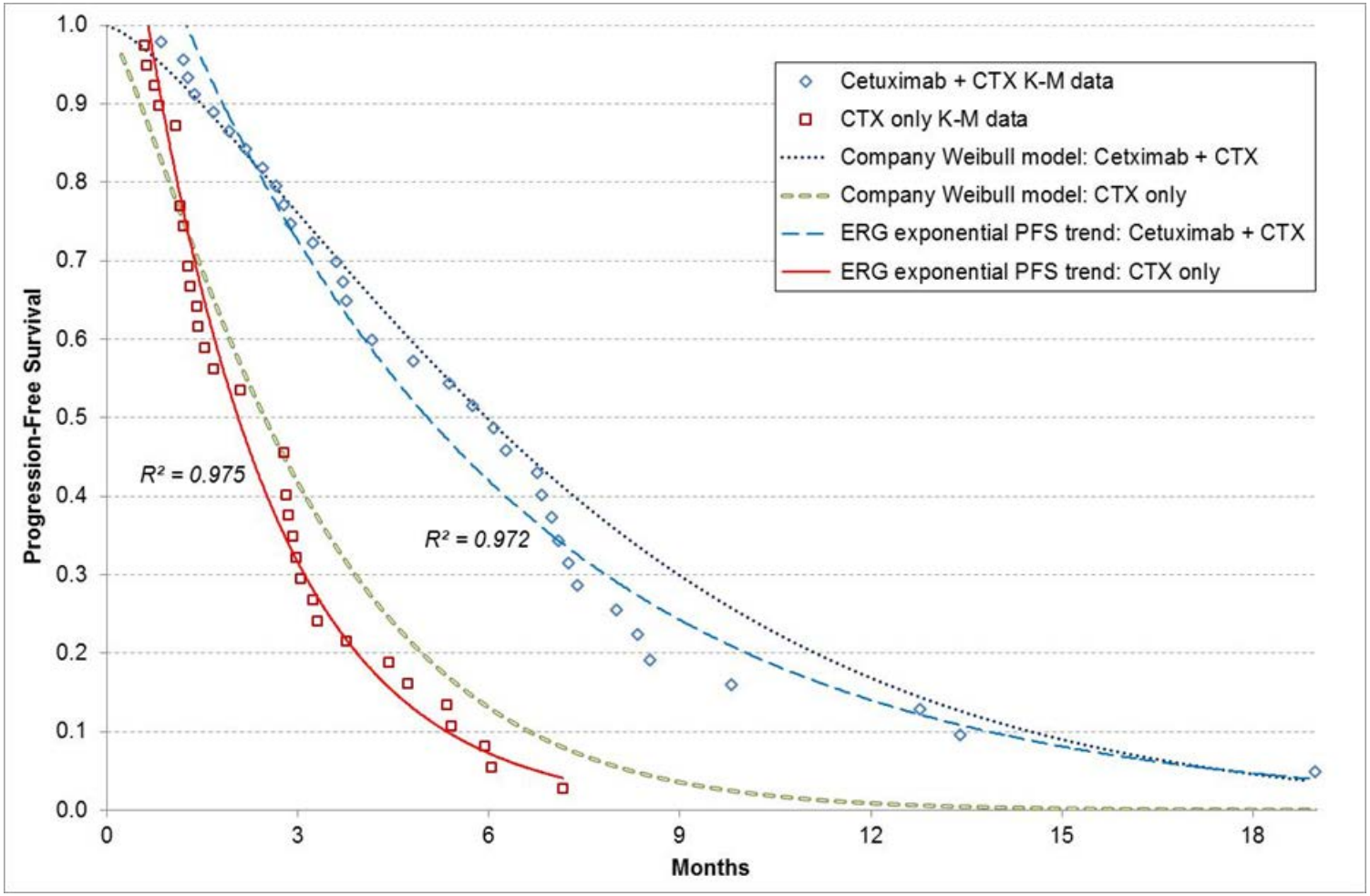
ERG critique

- Changes from TA172 : Oral cavity only – a small subgroup (88 of 442 patients)
- Modelling of progression-free survival and overall survival
- Post-progression survival
- Drug acquisition costs and BSA
- Cisplatin versus carboplatin
- Utility values
- Vial reconciliation

ERG's critique
Changes from TA172

- Focus on oral cavity subgroup
  - On request the company provided information specific to the oral cavity subgroup of the EXTREME clinical trial
    - Full Kaplan-Meier (K-M) analysis results showing K-M survival estimates at each event time, for both treatment arms in the EXTREME trial for overall survival
    - Progression-free survival using the most recent data cut and based on the investigator assessment of disease progression
- Current company model has been calibrated against extended 5-year follow-up data

Company and ERG modelling of progression-free survival



CTX=cisplatin or carboplatin plus fluorouracil

K-M=Kaplan-Meier analysis

Source: Figure 2, page 11 of the ERG report

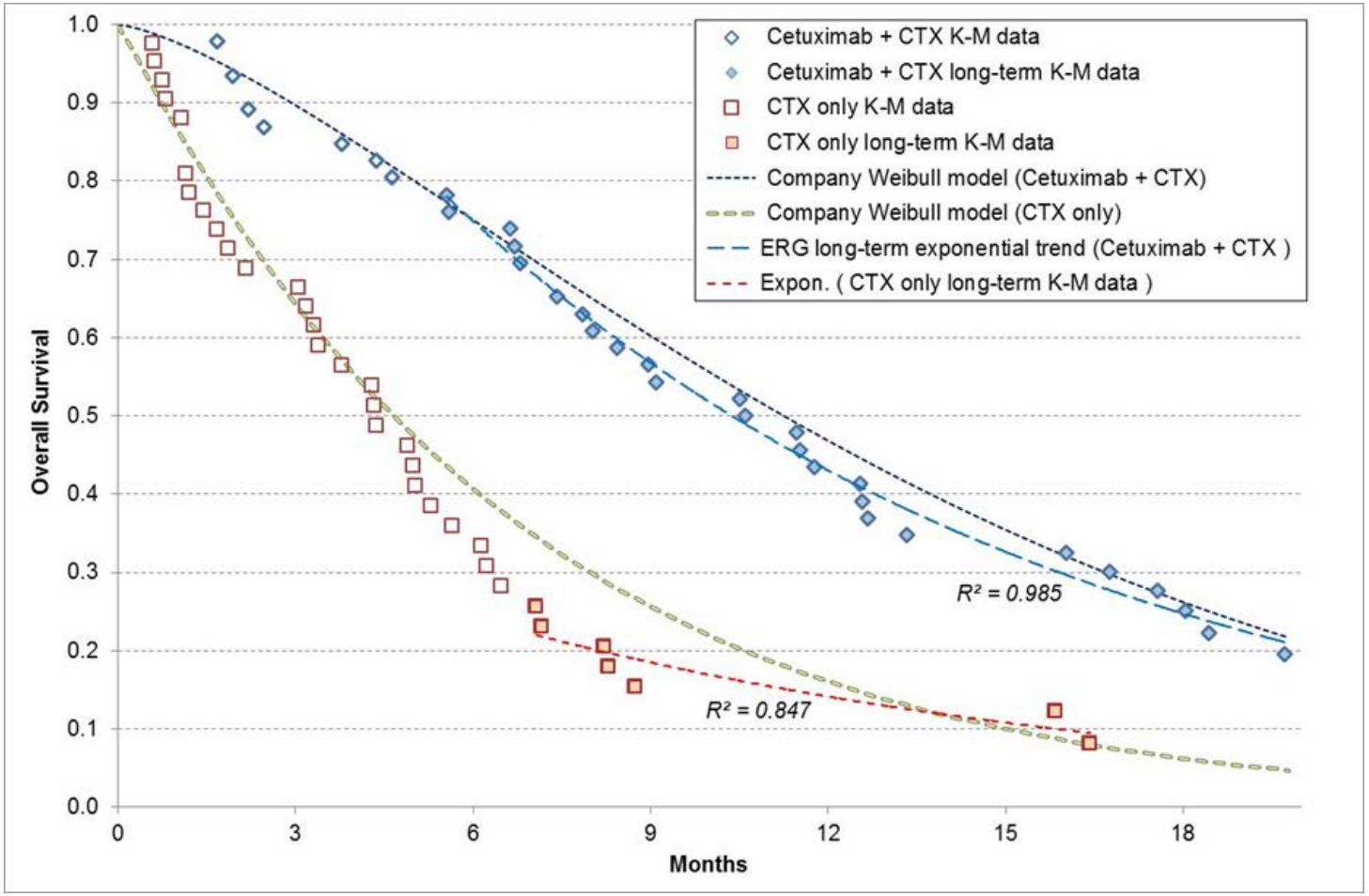
ERG critique
Mean progression-free survival

Estimation method	Cetuximab + chemotherapy* (months)	Chemotherapy* only (months)	Mean PFS gain (months)
Company base case	7.52	3.49	+ 4.03
ERG PFS analysis	7.31	3.22	+ 4.09

*Chemotherapy=cisplatin or carboplatin plus fluorouracil

Source: Table 3, page 10 of the ERG report

Company and ERG modelling of overall survival



CTX=cisplatin or carboplatin plus fluorouracil

K-M = Kaplan-Meier analysis

Source: Figure 4, page 13 of the ERG report

ERG's critique
Post-progression survival

- The difference between OS and PFS estimates implies that between 36% (ERG estimate) and 40% (company model) of the OS estimated gain from treatment with cetuximab occurs after disease

ERG critique
Mean overall survival

Estimation method	Cetuximab + chemotherapy* (months)	Chemotherapy* only (months)	Mean OS gain (months)
Company base case	13.68	6.95	+ 6.72
ERG OS analysis	13.51	7.12	+ 6.40

*Chemotherapy=cisplatin or carboplatin plus fluorouracil

Source: Table 4, page 12 of the ERG report

ERG critique
Drug acquisition costs

- The company submission follows TA172 i.e.
  - Mean EXTREME trial BSA applied to all patients
  - No adjustment for gender difference in BSA or UK audit data
- The ERG uses BSA from head and neck cancer chemotherapy patients at 3 UK cancer centres[1] with further adjustment for gender mix
- The ERG prefers either the cost estimated using the gender mix from the EXTREME clinical trial for consistency with other trial data, or the UK audit study[1] to match a relevant UK patient population
- The ERG estimates of the cost of cetuximab exceed the company estimates but almost all other costs are lower in the ERG estimate

[1]*Sacco et al., 2008 unpublished*

ERG critique
Cisplatin versus carboplatin

- Clinical advice indicates that cisplatin is used in almost all cases in the UK
- On this basis the ERG considers it appropriate to assume that 100% patients receiving platinum therapy will receive cisplatin

ERG critique
Utility values

- The company states that separate treatment-specific utility estimates should be used pre-progression
  - There are better response rates for cetuximab than standard of care
  - Cetuximab has a better adverse event profile than standard of care
- The ERG considers that there is no strong evidence to support the use of treatment-specific utility values in the decision model
  - It is likely that the difference in the estimated utility values based on limited transformed trial quality of life data is largely an artefact of random variation
  - The estimated utility values are based on available data from the whole trial population. If symptom scores from the oral cavity cancer subgroup had been used, the balance of estimated pre-progression utility estimates may have been very different in either direction

Utility values by disease status

	Utilities	
	Stable/response	Progressive disease
Cetuximab + chemotherapy*	0.69	0.53
Chemotherapy* only	0.65	0.51
Overall (independent of treatment)	0.67	0.52

*Chemotherapy=cisplatin or carboplatin plus fluorouracil

- The company model uses separate treatment-specific utility values pre-progression
- The ERG model uses common utilities in both treatment arms

ERG critique
Vial reconciliation

- The company model corrects for a mismatch between the predicted number and actual number of cetuximab vials used per cycle in the EXTREME trial
- The adjustment assumes that a fixed number of vials are used per dose
- But doses may vary and this approach cannot be validated (without patient level data access)
- Over time the ERG expect the ‘adjustment factor’ would diverge unpredictably from the simple assumption of a constant fixed dose
- Disabling this adjustment has a significant effect on the estimated deterministic ICER

Deterministic cost effectiveness ERG revisions to company base case

Model scenario	Incremental Cost	Incremental QALYs	ICER Per QALY	ICER Change
A. Company base case	[redacted]	0.353	[redacted]	-
R1) ERG revised drug costs:	[redacted]	0.353	[redacted]	[redacted]
a) EXTREME trial gender mix	[redacted]		[redacted]	[redacted]
b) UK audit gender mix	[redacted]		[redacted]	[redacted]
c) NCIN gender mix	[redacted]		[redacted]	[redacted]
R2) ERG revised PFS estimates	[redacted]	0.353	[redacted]	[redacted]
R3) ERG revised OS estimates	[redacted]	0.339	[redacted]	[redacted]
R4) Apply 100% cisplatin use	[redacted]	0.353	[redacted]	[redacted]
R5) Common pre-progression utility value	[redacted]	0.336	[redacted]	[redacted]
R6) Disable cetuximab reconciliation adjustment	[redacted]	0.353	[redacted]	[redacted]
B. ERG revised base case (A+R1a/b/c, R2 – R6; all revisions and listed by EXTREME trial, UK audit and NCIN gender mix)	[redacted]	0.323	[redacted]	[redacted]

Source: Table 6, page 17 of the ERG report; NCIN=National Cancer Intelligence Network

CDF reconsideration
Issues for consideration

- The submission is focussed on the oral cavity subgroup
  - Does the Committee consider this appropriate given the small subgroup size (n=46 versus 42)?
- Are the ERG adjustments preferable? In particular, is the dose reconciliation for the mismatch between the predicted and actual number of vials of cetuximab appropriate?
- Which ICER estimates are most plausible?

Note: The patient access scheme is subject to positive guidance for cetuximab as a first-line treatment for metastatic colorectal cancer (ongoing MTA review; expected publication date Nov 2016)

Back-up slides

Limitations of the EXTREME trial

- Open label study
- Representative of UK patients?
  - Only 9 patients recruited in the UK
  - Other patients considered by the committee to be younger and fitter (KPS score >80 in 88% patients) that UK patients
- n=88 in the oral cavity cancer subgroup

Cetuximab in recurrent/metastatic SCCHN: Other clinical studies

- DIRECT prospective, observational, single arm study (n=154)[1]
  - Same dosing regimen as EXTREME
  - Confirmed feasibility and tolerance
  - Survival outcomes not reported in the conference abstract
- TPExtreme phase II, single arm study (n=54)[2]
  - Cetuximab plus **docetaxel** and cisplatin for 4 cycles plus cetuximab monotherapy every 2 weeks until progression
  - Median OS 14 months, median PFS 6.2 months, ORR 44.4%
- TPEX retrospective, observational, single arm study (n=30)[3]
  - Same dosing regimen as TPExtreme
  - Median OS 13.6 months, median PFS 6.0 months, ORR 87%

[1]Guigay et al. (2014) Annals of Oncology; [2]Guigay et al. (2015) Annals of Oncology; [3]Even at al. (2014) 39th EMSO congress

Considerations in existing guidance and company submission – Subgroup analysis

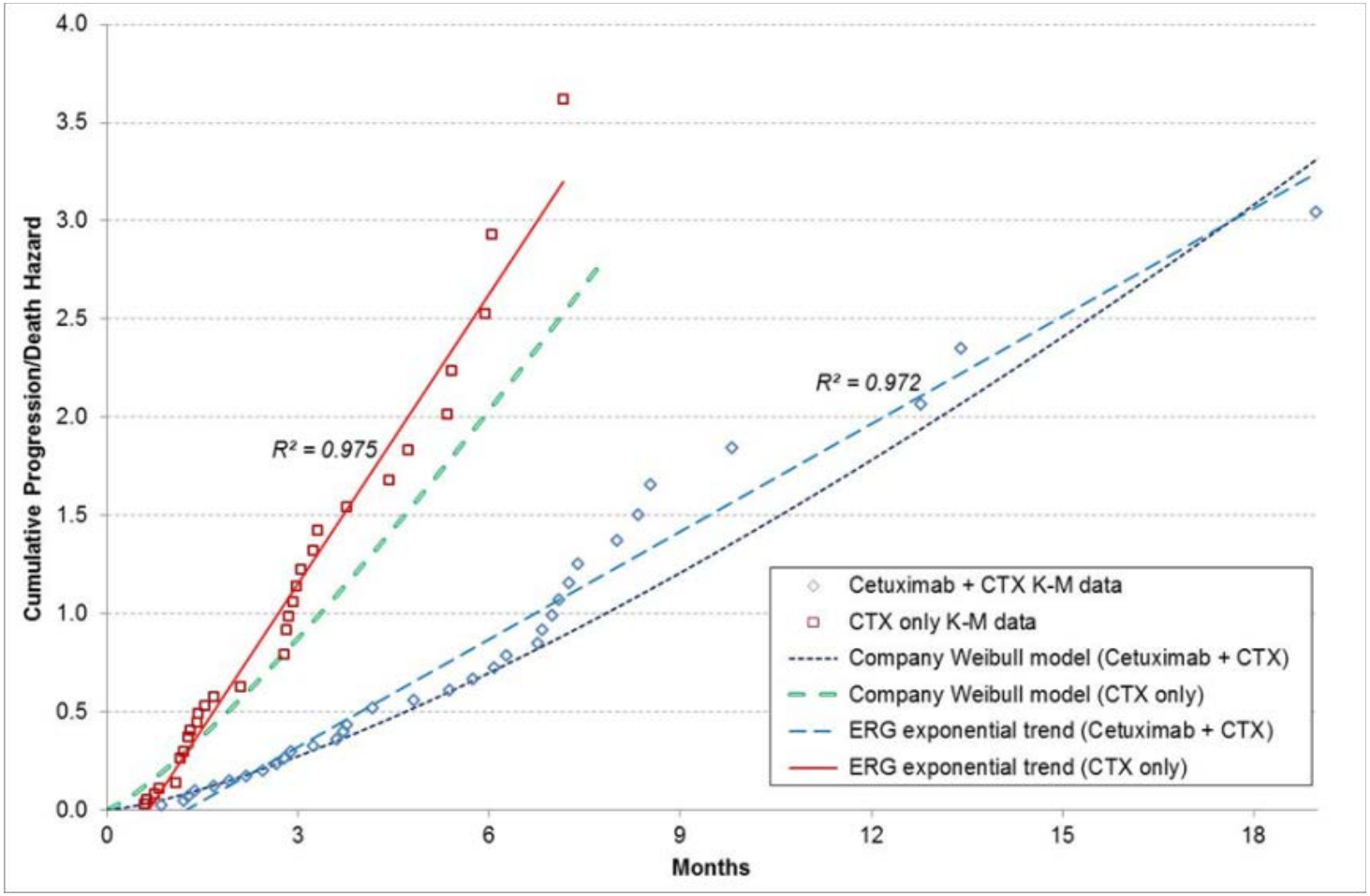
NICE guidance	Company submission	Supporting evidence
• Committee not persuaded that the evidence supported using the subgroup estimate for clinical effectiveness • Clinical experts stated that 'patients with tumours in the oral cavity have a relatively favourable prognosis compared with the average prognosis for recurrent and/or metastatic SCCHN'	• Makes a case for the poor prognosis for this patient population • Little chance of becoming cost effective in the overall population	• Combined data from 2 RCTs of patients (n=399) with recurrent head and neck cancer treated with cisplatin-based combination chemotherapy - 'median survival in patients with oral cavity or hypopharyngeal cancers was 0.52 years compared to 0.70 years in patients with other head and neck cancers (p=0.04)' • Reference to clinical expert testimony – data held by the company and not available to the ERG

Considerations in existing guidance and company submission – End of life

TA172 committee considerations	Company submission	Supporting evidence
• Considered criteria for the whole cohort because the subgroup data was not considered to be robust • Considered life expectancy likely to be less than 24 months but overall survival gain of 2.2 months was not in keeping with the criteria relating to extension of life	• EXTREME trial demonstrate end of life benefits	• EXTREME trial shows patients with an oral cavity tumour having cetuximab have significant incremental delay in progression (median PFS of 3.3 months) and incremental improvement in overall survival (median OS of 6.6 months) beyond the 3 months required to meet the end of life criteria • Additional data from a single arm trial of patients (n=54) that received combination treatment and reported median OS of 14 months[1]

[1]*Guigay et al. (2015) Annals of Oncology*

Company and ERG modelling of PFS cumulative hazard data

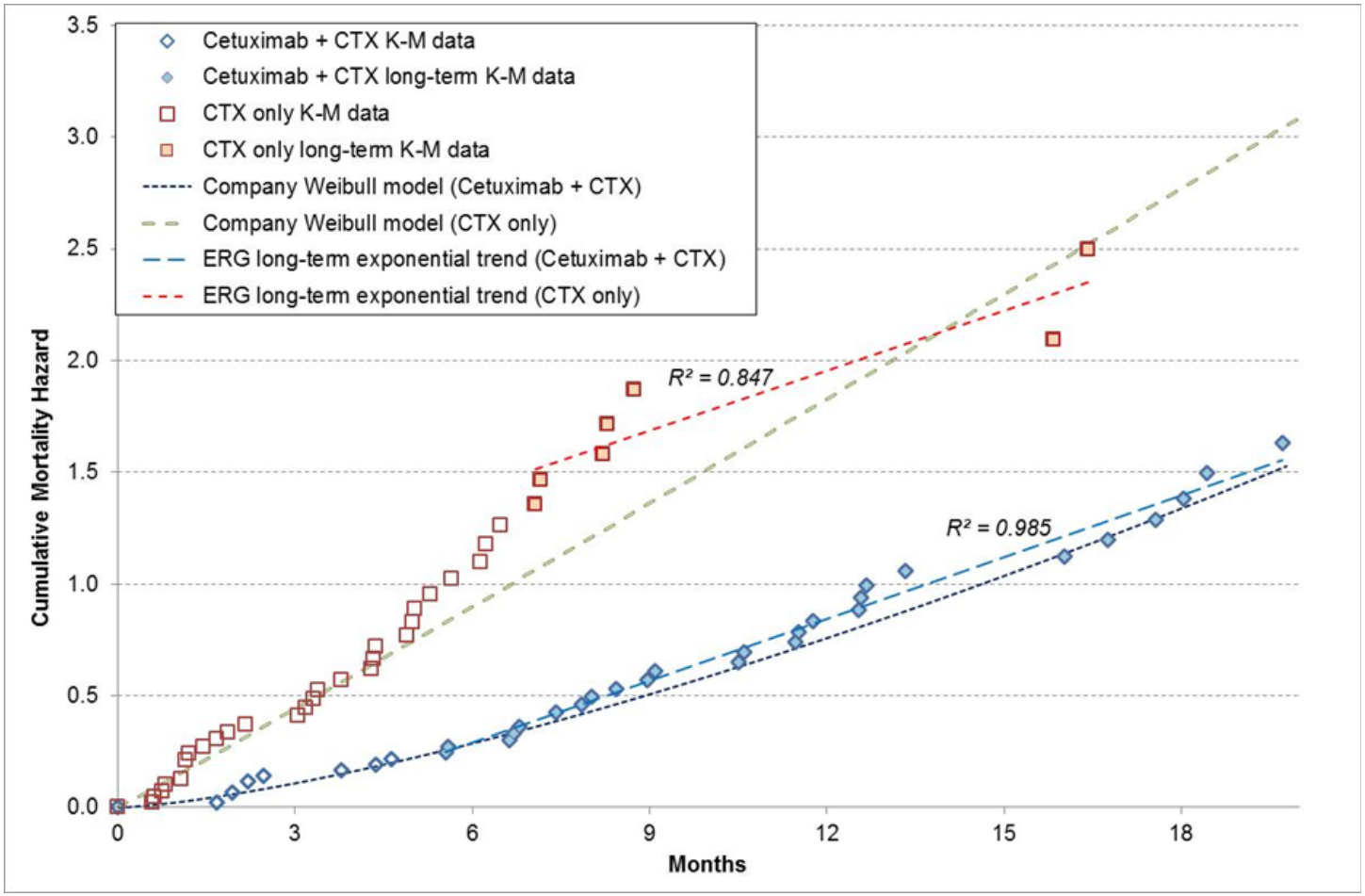


CTX=cisplatin or carboplatin plus fluorouracil

K-M=Kaplan-Meier analysis

Source: Figure 1, page 11 of the ERG report

Company and ERG modelling of overall survival cumulative hazard data



CTX=cisplatin or carboplatin plus fluorouracil

K-M=Kaplan-Meier analysis

Source: Figure 3, page 12 of the ERG report

Drug costs

- The company notes that:
- ‘[redacted]’

Deterministic cost effectiveness ERG revisions to company base case

Model scenario	Cetuximab + CTX		CTX		Incremental		ICER	
ERG revision	Cost	QALYs	Cost	QALYs	Cost	QALYs	Per QALY gained	Change
A. Company base case	[redacted]	0.673	[redacted]	0.319	[redacted]	0.353	[redacted]	-
R1) ERG revised drug costs:								
a)trial gender mix	[redacted]	0.673	[redacted]	0.319	[redacted]	0.353	[redacted]	[redacted]
b)UK audit gender mix	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
c)NCIN gender mix	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
R2) ERG revised PFS estimates	[redacted]	0.670	[redacted]	0.317	[redacted]	0.353	[redacted]	[redacted]
R3) ERG revised OS estimates	[redacted]	0.664	[redacted]	0.325	[redacted]	0.339	[redacted]	[redacted]
R4) Apply 100% cisplatin use	[redacted]	0.673	[redacted]	0.319	[redacted]	0.353	[redacted]	[redacted]
R5) Common pre-progression utility value	[redacted]	0.661	[redacted]	0.325	[redacted]	0.336	[redacted]	[redacted]
R6) Disable cetuximab reconciliation adjustment	[redacted]	0.673	[redacted]	0.319	[redacted]	0.353	[redacted]	[redacted]
B. ERG revised base case	[redacted]	0.650	[redacted]	0.327	[redacted]	0.323	[redacted]	[redacted]
A+R1a/b/c, R2 – R6	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]

Source: Table 6, page 17 of the ERG report; NCIN=National Cancer Intelligence Network

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Submission template for the re-consideration of current CDF technologies under the new proposed CDF criteria

Cetuximab for the treatment of recurrent/metastatic head and neck cancer

16th May 2016

1 Details of the patient access scheme/ commercial access agreement

1.1 Please give the name of the technology and the disease area to which the patient access scheme/ commercial access agreement applies.

A revised simple discount has been agreed with the Department of Health and communicated with NICE as part of the ongoing MTA for cetuximab (Erbitux®) as a first line treatment of metastatic colorectal cancer. This revised PAS will apply from the time of/in the case of positive guidance for mCRC and will subsequently cover all reimbursed indications for cetuximab (Erbitux®), including that under consideration in this re-submission

1.2 Please outline the rationale for developing the patient access scheme/ commercial access agreement.

The patient access scheme – a simple discount off the list price of cetuximab (Erbitux®), applied at the point of invoicing – was proposed by Merck in order to offer the NHS value for money, as determined by cost-effectiveness in the mCRC MTA and in this current technology appraisal.

1.3 Please describe the type of patient access scheme (as defined by the PPRS)/ commercial access agreement.

The patient access scheme is a simple scheme whereby Merck is offering a discount at the point of invoice. Implementation of this patient access scheme will not incur any administrative burden for the NHS.

1.4 Please provide specific details of the patient population to which the patient access scheme/ commercial access agreement applies. Does the scheme apply to the whole licensed population or only to a specific

subgroup (for example, type of tumour, location of tumour)? In case of the latter, please state:

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

Eribitux® will be provided under the existing patient access scheme, to eligible patients across all reimbursed cetuximab indications. For the purpose of this submission we are focusing on the treatment of SCCHN in combination with platinum-based chemotherapy for recurrent and/or metastatic disease for the oral cavity subgroup.

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

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

The patient access scheme will be implemented conditional upon and from the time of positive NICE guidance for cetuximab (Erbitux®) as a first line treatment for mCRC (the ongoing MTA)

1.6 What proportion of the patient population (specified in 3.4) is expected to meet the patient access scheme/ commercial access agreement criteria (specified in 3.5)?

All patients prescribed cetuximab for indications listed above will be eligible to receive the drug via the patient access scheme agreed by the Department of Health i.e. 100% of patients will receive the drug at the new proposed price.

1.7 Please explain in detail the financial aspects of the patient access scheme/ commercial access agreement. How will any rebates be calculated and paid?

Not applicable. This patient access scheme is operating as a simple scheme which involves a discount at the point of invoice. It will not involve any rebates.

1.8 Please provide details of how the patient access scheme/ commercial access agreement will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

Not applicable. This patient access scheme is operating as a simple scheme which involves a discount at the point of invoice. No additional information will need to be collected and there will be no administrative burden associated with this scheme for the NHS.

1.9 Please provide a flow diagram that clearly shows how the patient access scheme/ commercial access agreement will operate. Any funding flows must be clearly demonstrated.

Not applicable.

1.10 Please provide details of the duration of the patient access scheme/ commercial access agreement.

The patient access scheme will remain in place until NICE undertake a review of either the mCRC or the RM SCCHN guidance.

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

There are no equity or equality issues related to this patient access scheme. The discount applies to all eligible patients at the point of invoice.

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

Not applicable. No documentation required for this simple scheme.

1.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix 5.2.

Not applicable

2 Clinical Evidence

The focus of this submission is the oral cavity subgroup of RM SCCHN. This section has been added to the template to allow a discussion of the clinical evidence behind and rationale for this restriction.

2.1 Introduction

Head and neck (H&N) cancer is a relatively uncommon cancer with approximately 8,100 new cases per year in England and Wales (HSIC, 2012). Head and neck cancers include cancers of the upper aerodigestive tract (including the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx), the paranasal sinuses, and the salivary glands. The anatomical sites affected are important for functions such as speech, swallowing, taste, and smell, so the cancers and their treatments may have considerable impact on important organ function with subsequent impairment of quality of life. Decisions about treatment are usually complex, and they must balance efficacy of treatment and likelihood of survival, with potential functional and quality of life outcomes (Mehanna, 2010).

The majority or about 90% of head and neck cancers are squamous cell carcinomas (SCCHN) (Döbrossy, 2005; NCCN, 2015). Squamous cell carcinoma most commonly arises in the oral cavity (mouth), throat (pharynx) and voice box (larynx) with oral cavity cancer being one of the most common types of head and neck cancer accounting for approximately 30% of all SCCHN (HSCIC, 2012). In 2011 in England and Wales over 2,000 people were diagnosed with oral cavity cancer, 60% of which were men (NCIN, 2013).

Surgery and radiotherapy are the treatment modalities for early stage disease and their use vary according to the site of the tumour and the need for organ and function preservation; for example radiotherapy instead of surgery to preserve the tongue for swallowing, or preserve the larynx for a patients voice (ACS, 2016 (Accessed)). More advanced H&N cancer is treated with a combination of surgery, radiation, chemotherapy, targeted therapy or palliative care. The mainstay of chemotherapy is predominantly platinum-based, either

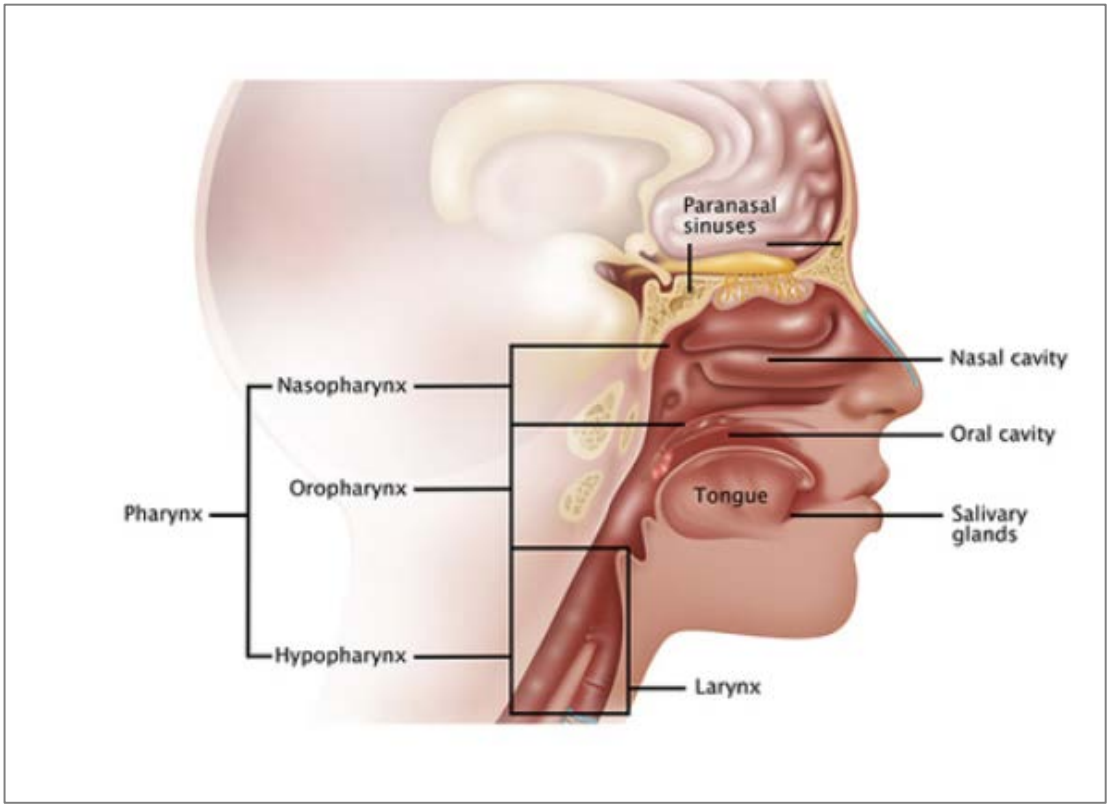
cisplatin or carboplatin, which highlights the lack of advance in therapeutic strategies. Data from the 2012 National H&N cancer audit highlight that crude survival rates are poor stating that '20 per cent of all head and neck cancer patients are deceased within a year of diagnosis and 30 per cent by two years' (HSIC, 2012).

In 2008, cetuximab was shown to improve overall survival in patients with advanced head and neck cancer when added to their standard chemotherapy. This was a major advance for the management of H&N cancer patients and has since become standard of care. In a report from the American Society of Clinical Oncology published in 2009, it was noted that the EXTREME study was '*the first randomized clinical trial in more than 30 years to demonstrate an improvement in overall survival for advanced head and neck cancers*' (Patrelli, 2009).

2.2 Aetiology of SCCHN

The main risk factors for SCCHN are tobacco use, heavy alcohol consumption and the chewing of tobacco or paan (areca nut/betel leaf). There is also an increase in the incidence of human papilloma virus (HPV)-associated SCCHN which is linked to sexual contact. Other risk factors include environmental toxins, poor oral hygiene, genetic predisposition and ultraviolet radiation, the latter particularly in the case of cancers of the lip (MacMillian, Accessed 2016). An overview of the anatomy of where SCCHN can occur is shown in Figure 1. (MacMillian, Accessed 2016)

Figure 1: Key areas where squamous cell cancers of the head and neck can occur



2.3 Recurrent Metastatic (RM) SCCHN

About a third of patients present with early stage disease, approximately half present with locally advanced disease (LA SCCHN) and 10% with recurrent or metastatic (RM SCCHN) (Jemal, 2008; Gold, 2009, March). A key issue in SCCHN pathogenesis is that the cancer develops within large areas of the mucosal epithelium which often extend into the surgical margins when tumours are excised, and can cause local recurrences and second primary tumours. (Leemans, 2011). This results in at least 50% of patients with locally advanced SCCHN developing locoregional recurrence or distant relapses. These patients are then considered to be RM SCCHN (Argiris, Head and neck cancer, 2008; Pignon, 2009; Spector, 2012).

2.4 Oral Cavity SCCHN

The focus of this submission is the oral cavity subgroup of RM SCCHN. Cancer of the oral cavity may not be recognised by the patient, particularly in the early stages when there may be limited pain or symptoms, and so it can frequently prosper (Foundation, 2016). Oral cancer also has a high risk of producing second, primary tumours when they recur. For these reasons, patients with recurrent and/or metastatic oral cavity SCCHN generally present with larger more advanced stage tumours.

Whilst the clinical evidence suggests that cetuximab is effective across the whole of the H&N cancer population, and is the standard of care in this patient group, we have taken a restricted approach to the cost-effectiveness analysis. Modelling indicates a low likelihood of cost-effectiveness in the broad population driven by non-drug (large administration) costs and is consistent with the DSU's own analysis of this decision problem. This is a pragmatic approach in the context of an effective therapy, which we hope will secure a positive outcome in a subgroup of patients with extremely high unmet need.

Survival rates for oral cavity cancer have remained static (Furness, 2010; Chinn, 2015). A study evaluating independent unfavourable prognostic factors for overall survival and time to disease progression identified "primary tumour in the oral cavity" as one such factor. In this study, median survival in patients with oral cavity or hypopharyngeal cancers was 0.52 years compared to 0.70 years in patients with other head and neck cancers (p=0.04) (Argiris, 2004).

2.5 The role of the EGFR in Oral Cavity SCCHN

While 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 shown in oral cavity tumours and 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 et al. showed that EGFR overexpression in oral cavity tumours of

young adults predisposes to a poor prognosis with a consequent adverse survival (Thomas, 2012).

2.6 Cetuximab (Erbitux) in SCCHN

Cetuximab (Erbitux®) is a chimerised monoclonal antibody to the Epidermal Growth Receptor (EGFR). By blocking EGFR in tumour cells, it decreases proliferation of cancer cells and causes shrinkage of the tumour (Lee, 2011). Cetuximab is licensed for use in both locally advanced and recurrent metastatic SCCHN (SPC, 2016). In addition, cetuximab is a chimeric (part mouse, part human) IgG2 antibody which has been shown to activate antibody dependent cellular cytotoxicity (ADCC), an additional mechanism whereby it can activate the immune system to recruit natural killer cells which have the ability to lyse tumour cells (Rivera, 2008). This dual mechanism of action of cetuximab of both blocking the EGFR and activation of ADCC are thought to contribute to the efficacy of cetuximab. Panitumumab is a second anti-EGFR antibody. In contrast to cetuximab, panitumumab is a fully-humanised IgG2 antibody and is not thought to activate ADCC.

The cetuximab data in the RM SCCHN setting is from the pivotal phase III clinical trial EXTREME (Vermorken, 2008). The EXTREME trial evaluated the addition of cetuximab to standard treatment with cisplatin/carboplatin + 5FU compared to platinum-based chemotherapy alone (CTX). The details of the EXTREME trial are described in detail in the previous TA172 submission and the key efficacy results are summarised below.

Table 1: Results for the ITT population in the EXTREME Trial.

Treatment Outcome	**CTX (220)**	**Cetuximab & CTX (222)**	
Overall Survival	7.4	10.1	HR 0.80 (95% CI: 0.64–0.99) p=0.04
Progression Free Survival	3.3	5.6	HR: 0.54 (95% CI 0.43–0.67) p<0.001
Overall Response Rate	20%	36%	OR: 2.33 (95% CI 1.50–3.60) p<0.001
Disease Control	60%	81%	OR: 2.88 (95% CI 1.87–4.44) p<0.001

CI: confidence interval; HR: hazard ratio; OR: odd's ratio,

As can be seen in Table 1, all of the efficacy endpoints in the ITT population from the EXTREME trial were statistically significantly in favour of cetuximab/chemotherapy when compared to treating patients with chemotherapy alone. This was the first trial to show a significant improvement in overall survival for RM SCCHN patients beyond that achieved with chemotherapy alone, showing an increase from 7.4 to 10.1 months – a statistically and clinically significant difference of 2.7 months (p=0.036). The median overall survival of 7.4 months in the chemotherapy-alone group is consistent with the results of other randomized trials (Forastiere, 1992; Jacobs, 1992). The results from this study were deemed to be a "major advance" in the treatment of head and neck cancers in a report from the

American Society of Clinical Oncology (ASCO) in 2009 (Patrelli, 2009). Cetuximab is considered to be standard of care today as highlighted in a recent review of treatment options for RM SCCHN in the Journal of Clinical Oncology 2015 “The only regimen to demonstrate survival superiority is platinum, 5 FU and cetuximab” (Sacco A. , 2015).

In addition, cetuximab is recommended in numerous guidelines worldwide (NCCN, 2015; Gregoire, 2010; Parikh, 2016).The combination of cetuximab with platinum-based chemotherapy is the only regimen to receive a Category 1 Evidence recommendation for the treatment of RM SCCHN by the NCCN. It is also the first line option recommended by the European/ESMO clinical practice guidelines (NCCN, 2015; Gregoire, 2010)

2.7 Cetuximab in Oral Cavity SCCHN

Cetuximab has proven efficacy for all patients with SCCHN in both the locally advanced (LA) and RM settings (Bonner, 2006; Vermorken, 2008). We acknowledge that although there is benefit for patients in the wider population of RM SCCHN, in the current model there is little chance of becoming cost effective in the overall population. Therefore, in order to find a route to cost effectiveness for RM SCCHN patients, the focus of this submission is the oral cavity subgroup, which as outlined earlier, have a poorer prognosis and a greater benefit from cetuximab compared to the other subgroups of SCCHN.

In patients with tumours of the oral cavity, cetuximab reduced the risk of death by 65% (HR 0.347, $p<0.0001$), resulting in an additional 6.6 months of overall survival, improving from a median OS of 4.4 months when treated with chemotherapy alone to 11.0 months when cetuximab is added to chemotherapy (Table 2). The data from the study support the real world findings that patients in this subgroup have a worse prognosis; oral cavity patients had a median OS of 4.4 months compared to 7.4 months in the ITT when treated with chemotherapy alone. This is supported by reports that oral cavity squamous cell carcinomas may be less sensitive to chemotherapy and radiation, relative to oropharyngeal or laryngeal cancers (Deschler, 2008).

This finding is also consistent with the previously mentioned data from Argiris outlining the reduced OS in these patients compared to the patients with other H&N cancers (Argiris, 2004).

In addition to the overall survival benefit seen, median progression free survival (PFS) is increased by 3.3 months with the addition of cetuximab to chemo, from 2.8 months to 6.1 months. Best overall response is improved by over [redacted] in this group, increasing from [redacted] with chemotherapy alone to [redacted] with cetuximab/chemo. This is of particular importance for these patients where tumour shrinkage and debulking plays a major role in organ function, pain, discomfort and quality of life. In addition, in the oral cavity group, [redacted] of patients achieved a complete response. In contrast, no patients achieved a complete response in the chemotherapy alone arm. The disease control rate was almost doubled by treatment with cetuximab/chemo compared to chemo alone. The subgroup analyses from the EXTREME study are show in Figure 2 and the benefit in the oral cavity subgroup can be clearly seen.

Table 2: Results for the oral cavity population in the EXTREME Trial.

	CTX (42)	**Cetuximab & CTX (46)**	**HR (95% CI)**
Overall Survival	4.4	11.0	0.42 (0.26–0.67)
Progression Free Survival	2.8	6.1	0.34 (0.21–0.55)
Best overall response rate (%, 95% CI)	[redacted]	[redacted]	N/R
Disease control rate (%, 95% CI)	[redacted]	[redacted]	N/R

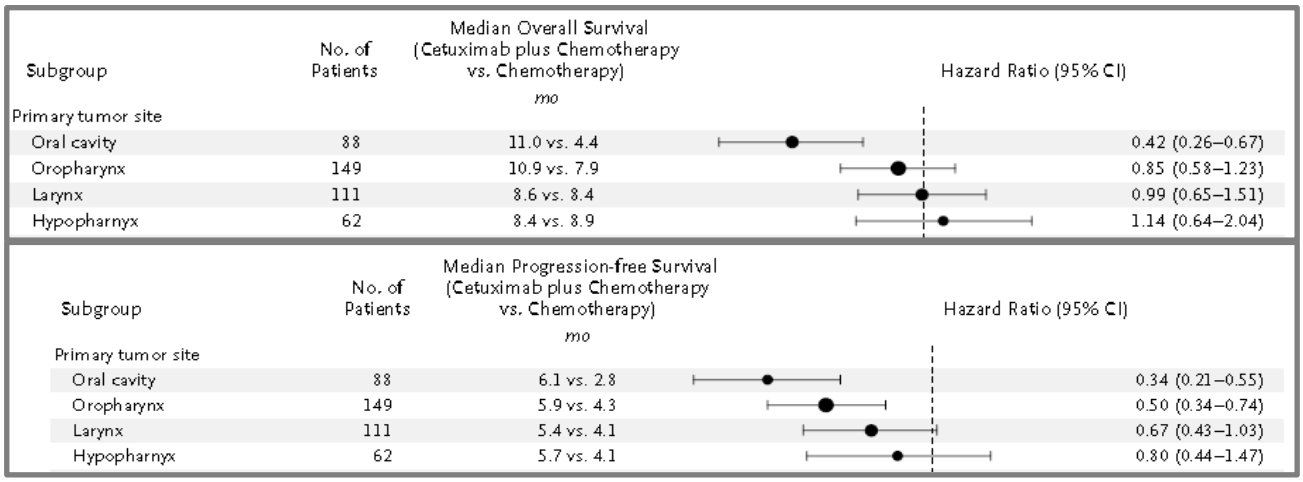
CI: confidence interval; HR: Hazard ratio;

In TA172, the oral cavity sub-group of patients was discussed. However, there was limited focus on the clinical rationale for improved outcome with cetuximab in this patient population, leading to concern around the reliability of the data generated from the protocol defined sub-group analysis. While it is important to interpret such sub-group data cautiously Merck believes that a

clinical rationale has been articulated and is supported by expert testimony (Data_On_File, 2016). Importantly, a similar pattern of magnified benefit in the oral cavity subgroup was observed in the SPECTRUM study, a large randomised phase 3 study assessing the efficacy of another anti-EGFR, panitumumab (Vermorken, 2013).

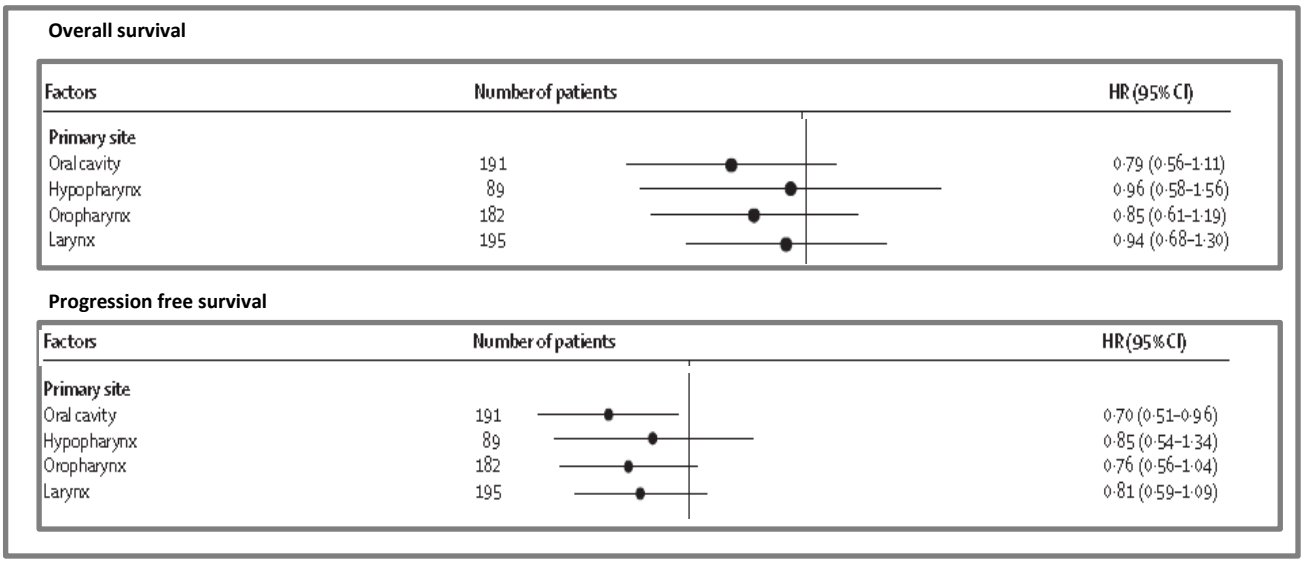
Panitumumab is a fully humanised IgG2 monoclonal antibody directed against the EGFR. In contrast, cetuximab is a chimeric IgG1 antibody. The chimeric nature of the cetuximab antibody and its innate ability to stimulate antibody dependent cellular cytotoxicity (ADCC) are thought to enhance its efficacy and differentiate it from panitumumab which doesn't induce ADCC (Rivera, 2008). Panitumumab has been studied in both LA and RM SCCHN and did not establish efficacy in either setting. Although panitumumab is less effective in the treatment of SCCHN than cetuximab, and has failed to demonstrate efficacy in the treatment of RM SCCHN patients, the greatest trend towards benefit was shown in the oral cavity sub-population. This supports the argument that the observed effect in the EXTREME study was clinically driven, rather than a chance finding.

Figure 2: Subgroup analyses from the EXTREME study.



The subgroup data from both the EXTREME and SPECTRUM studies are shown in Figure 2 and Figure 3.

Figure 3: Subgroup analyses from the SPECTRUM study.



The statistically and clinically significant improvements in response resulting from the addition of cetuximab to chemotherapy are particularly important for oral cavity patients, in whom tumour shrinkage can greatly benefit problems with functions such as breathing, talking and swallowing, and diminish malformation of the face and appearance (Licitra, 2015). In terms of halting the progression of disease, the odds of achieving disease control were seven times higher in patients treated with cetuximab (OR 7.2, p=0.0003 (Vermorken, 2008)). Case reports and expert testimony support these findings (Report, 2016) (Data_On_File, 2016). The safety profile of cetuximab was as expected and manageable.

As can be seen from the results, outcomes with cetuximab clearly surpass the thresholds for an end of life medicine with extremely low expected survival for these patients at around 4 months (median) OS for oral cavity patients or 7 months (median) for the ITT RM SCCHN population; in either case, this is significantly below the 2 years required by NICE. With the addition of cetuximab to chemotherapy, there is a significant 6 month median overall survival benefit for patients in the oral cavity subgroup, which meets the level of benefit required to be considered clinically significant.

In our previous submission, the Committee were unsure of the applicability of the subgroup analyses for the oral cavity subset. In this submission, we have presented data on both the oral cavity subgroup and their prognosis, the role of EGFR and data from 2 phase 3 clinical trials with anti-EGFRs in this patient population, in addition to expert opinion, we hope this concern will no longer be present.

2.8 Quality of Life

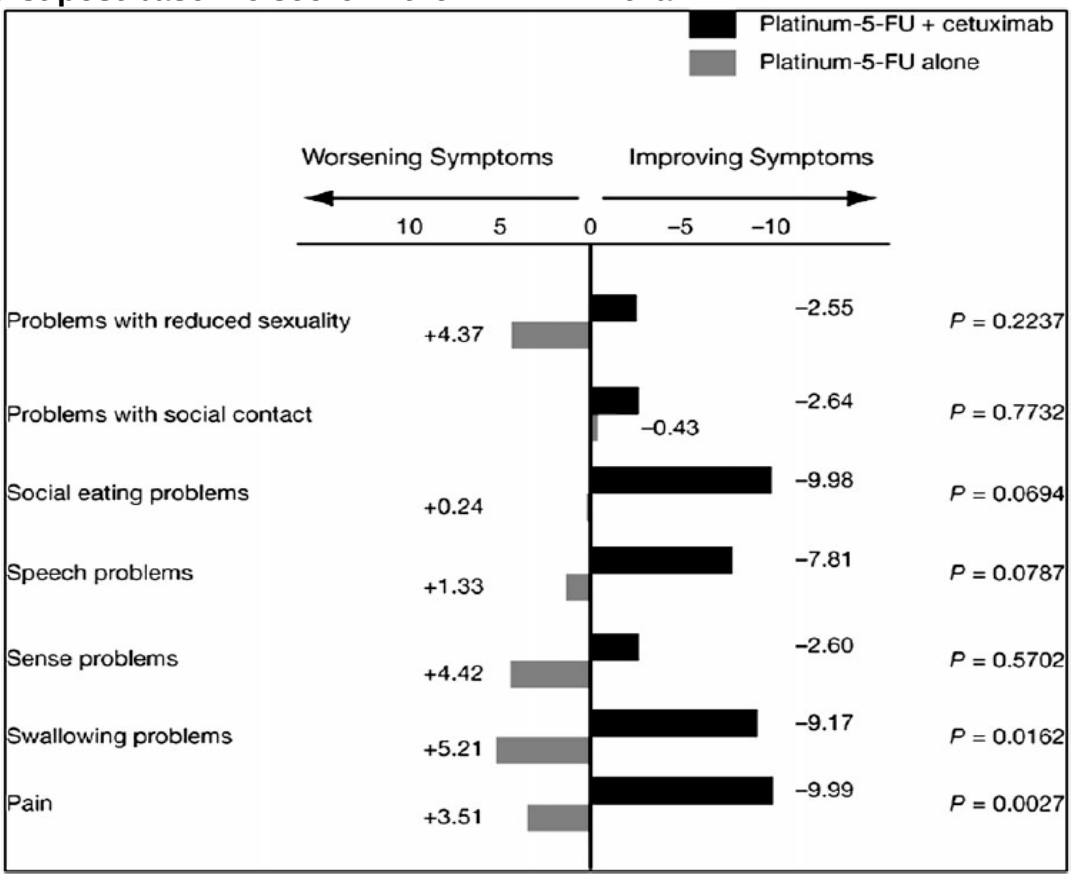
Head and neck cancers are particularly distressing to patients because of their daily impact not only on basic physiological functions such as breathing, swallowing, eating and balance, but also on the senses (taste, vision and hearing) and on the uniquely human and individualising characteristics of facial expression and voice (Licitra, 2015). Quality of life issues that are commonly reported include pain, mucositis, xerostomia (dry mouth), concern or embarrassment with speech or eating, particularly in public, as well as appearance dissatisfaction and body image concerns that have a marked impact on self-confidence, social functioning and on intimate relationships (Onakoya, 2006). Dysphagia, difficulties in swallowing, is regarded as the most common nutrition-related problem arising from the treatment of head and neck cancers. A common sequela of dysphagia is nutritional compromise leading to weight loss and malnutrition, which adds to the decline in overall well-being and quality of life, as well as leading to poorer responses to treatment and to an increase in the incidence of adverse events (Ehrsson, 2012; Languis, 2013). Patients with oral cavity cancer have been shown to have some of the greatest weight loss of head and neck cancer patients (Ehrsson, 2012).

In contrast to the negative effects of surgery and radiation therapy on oral tumours, the efficacy benefits of cetuximab do not appear to be achieved at the expense of quality of life (QoL).

In an analysis of QoL in the total population in EXTREME, there was a significant improvement in the global health status/QoL score in the cetuximab arm (p=0.0415) (Mesia, 2010). Symptom scores for problems associated with reduced sexuality, social contact, pain, swallowing, speech, sense problems and social eating all improved in the cetuximab arm, suggesting 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). Oral cavity cancers can spread to nearby bone and to the base of the tongue, resulting in severe pain and of course, swallowing may be impaired, both of these symptoms were significantly improved by treatment with cetuximab.

In contrast, treatment with chemotherapy alone resulted in worsening scores for all of these symptoms over time, with the exception of social contact, for which there was a negligible improvement. The contrast between symptom scores in the two treatment arms is summarised in Figure 4.

Figure 4: QLQ-H&N35 symptom scores: mean change from baseline to worst post baseline score in the EXTREME trial



Although QoL results are not available for the oral cavity subgroup patients specifically, it is reasonable to anticipate that, on the basis of the clinical results observed, that the impact of cetuximab on this endpoint would be comparable or improved. Symptoms linked to the oral cavity are likely to have a considerable impact on quality of life, and it is reasonable to expect that a treatment such as cetuximab, which appears highly efficacious at shrinking oral cavity tumours, would improve quality of life during treatment.

2.9 Further evidence of clinical efficacy of cetuximab

The results of the EXTREME trial are supported by additional studies which also showed benefit of cetuximab in combination with platinum based chemotherapy in RM SCCHN.

The DIRECT study was a real world observational study which assessed the cetuximab regimen used in the EXTREME trial. It suggests that the EXTREME trial results are applicable and that this regimen is utilised in the real world setting. Outcomes were similar to those achieved in EXTREME (Guigay, 2014). This is an important finding as it is often not the case that clinical trial results are replicated when the drug is used in routine clinical practice.

The TPExtreme study was a phase 2, single arm study run by the GORTEC group (Guigay, 2015). Patients were treated with cetuximab in combination with docetaxel and cisplatin for 4 cycles followed by cetuximab monotherapy until progression administered on a fortnightly basis. This study demonstrated a 14 month median overall survival, and 6.2 months median PFS (Guigay, 2015). In addition, an overall response rate of 44.4% was achieved highlighting the benefit for these patients in reducing tumour burden. Whilst the study is non-comparative, it may have value in triangulating the trial and the real world results. In the real world setting, the TPEx regimen was found to produce an 86% overall response rate and >13 months OS at a single centre (Even, 2014).

2.10 Cost Considerations

In the economic model (described below), assumptions around the dosing of cetuximab are explored. Market research data suggests that H&N cancer patients often receive cetuximab less frequently than on a weekly basis (often fortnightly and even every three weeks). (Data on File: Instar, June 2014) This is similar to the way that cetuximab is used in the NHS in patients with metastatic colorectal cancer. As in that case, Merck contends that a scenario analysis approximating the way that cetuximab is used in clinical practice (using market research data) more accurately reflects the true value of the treatment to the NHS. An assumption that each and every patient treated with cetuximab is receiving it on a weekly basis for the duration of their treatment is a conservative one. Perversely this affects the cost-effectiveness of

cetuximab more the less expensive cetuximab becomes because of the relative contribution of administration costs to the overall cost of treatment.

From a budget impact perspective, NICE approval for the oral cavity patient subgroup will have limited impact. Oral cavity patients represent around 30% of the SCCHN population. Based on 2015 CDF applications for the total RM SCCHN population, it is estimated that around 100 patients would be treated per annum (CDF, 2015).

2.11 Criticisms by the ERG of the clinical data in the previous submission

In the previous submission for TA172, the Committee were unsure of the validity of the results of the subgroup analyses, including that of the oral cavity subgroup.

Since 2008, there are a number of additional considerations relevant to this submission. As described previously, a similar pattern of magnified benefit in patients with tumours of the oral cavity has been observed in the SPECTRUM study (Vermorken el al 2013) of panitumumab (Vermorken, 2013). The chances that two studies of anti-EGFR treatment returned artefactual results in the same subgroup are slim and rather Merck believes the findings to be genuine. In this re-submission, Merck have presented a more complete discussion of the oral cavity patient subgroup and have provided a sound biological rationale for the relatively greater efficacy of cetuximab in these patients. We trust that the Committee will be satisfied that patients with tumours of the oral cavity represent a distinct group with a considerably high unmet need. This position is supported by UK clinical opinion.

Criticisms of the economic model structure and parameters are addressed in the economic section.

2.12 Conclusion

H&N is a complex cancer. Patients have limited treatment options and face a poor prognosis. Cetuximab is the only agent that has proven to improve outcomes for H&N cancer patients beyond chemotherapy alone. It has subsequently become the global standard of care. [redacted]

Cetuximab provides significant improvement to the oral cavity cancer patients, a patient group with a clear high unmet need. This is demonstrated by clinical data, and exemplified by case studies, where the use of cetuximab has helped patients avoid high morbidity surgery, resume normal eating and enjoy enhanced quality of life (Report, 2016). Having been available in the UK for several years through the CDF and via NICE for a limited sub group of locally advanced SCCHN patients, physicians are well versed in management of toxicities and no new toxicity or administration concerns are expected to emerge at this stage.

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.

3 Cost effectiveness

3.1 Please show the changes made to the original company base case to align with the assumptions that determined the most plausible incremental cost effectiveness ratio(s) as determined by the Appraisal Committee and presented in the published guidance. Provide sufficient detail about how the Appraisal Committee's preferred assumptions have been implemented in the economic model. Provide sufficient detail to allow the replication of the changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. No other changes should be made to the model.

For the purposes of this resubmission, the original cost-effectiveness model (submitted to NICE in 2008 during TA172) has been updated to address the key criticisms and comments relating to parameter estimation. The revised model assumptions have been listed in ***Table 3*** and an explanation for their use is provided below.

The original NICE submission included all recurrent and/ or metastatic (RM) SCCHN patients. Considering the statement made in the ERG report that cetuximab plus chemotherapy may not be cost-effective at any price the target population has been modified. As described in the clinical section above, the efficacy of cetuximab appears to be greatest among oral cavity patients. Given the clinical rationale for this superior treatment effect, and the high unmet need in this patient subgroup, this submission focuses on patients with RM SCCHN of the oral cavity.

If required, the results for the all RM SCCHN patient group can be generated in the model by selecting the "Patients with recurrent/ metastatic SCCHN" population in the "Model Parameters" worksheet (cell C9).

Table 3: Assumptions in the economic model

Parameter	Assumption by Merck in original model (2008, TA172)	Appraisal Committee's preferred assumption	Accepted (Y/N)	Assumption by Merck in this model	Justification
Body surface area of patients in model	BSA of 1.7m^2 used to calculate treatment dosing. Worksheet: "Unit costs"- Drug acquisition costs and Surgery and Radiation costs table	ERG recommended (ERG, 2008) BSA of 1.83 based on results of a UK audit study of general head and neck patients, weighted for the gender balance in the EXTREME trial.	N	Mean BSA from EXTREME trial (i.e. 1.75m^2) given that BSA for a RM SCCHN patient and not all head and neck patients	We believe the mean BSA from the EXTREME trial is more representative of a RM SCCHN patient. See explanation below under assumption 1
Pre-progression utility across the treatment arms	Treatment specific utilities were applied in the pre-progression health state Worksheet: "Model Parameters" worksheet cells C7:8	The ERG recommended using the same utility in each treatment arm in each health state	N	Treatment specific pre-progression utility (Cetuximab: 0.69 and standard of care: 0.65) from EXTREME trial	Cetuximab has a good response rate, reducing tumour size which influences QoL in the oral cavity subgroup. See explanation below under assumption 2.
Half cycle correction included	No half cycle correction included Worksheets: "Markov-Txarm1" and "MarkovTxarm2" cells BM209, BQ 209 in both	ERG recommended including a half cycle correction on the base-case results	Y	Merck have implemented a half cycle correction	N/A

Inconsistent price base	Chemotherapy Indicative Tariff (2007/08) for inpatient stay; NHS reference costs 2004 for outpatient visits; Personal Social Services Research Unit (PSSRU) 2007 for primary care costs and BNF 55 for drug costs. Worksheet: "Resource use and Cost" cells C96:C106	The ERG recommended using 2006/2007 NHS reference costs for inpatient, outpatient and investigations; Personal Social Services Research Unit (PSSRU) 2008 for primary care costs and BNF 56 for drug costs.	Y	In this submission, prices have been updated to reflect the latest costs available using the references suggested by the ERG: 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[1] (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)	N/A
Extrapolation of life years gained	Parametric survival projection models were applied to extrapolate outcomes by fitting Weibull curves	Unclear- the ERG replaced projection modelling of costs and outcomes with a comparison of costs and outcomes at 24 months (the end of the follow-up period in the EXTREME	N	Merck retain the original approach to extrapolation using the Weibull fitted curves.	Long term outcome data is discussed in relation to 5 year EXTREME follow-up data, now available. Model appears to have underestimated survival post 24 months (follow-up of

[1] Since updating the costs, a more recent version of the eMIT costs (updated to end of December 2015) have become available. The implementation of these (instead of those used here, updated to the end of June 2015), has minimal impact on the final ICER bringing it down by £101.

		trial)			EXTREME). See explanation below under assumption 5

Assumption 1: The mean body surface area (BSA) assumed to reflect patient population

The ERG (ERG, 2008) proposed using a BSA of 1.83m^2 (page 57 of ERG report), because they felt that Merck had underestimated the actual BSA for H&N patients in the UK. They suggested referencing BSA derived from a retrospective study of three UK centers (males: 1.85m^2; female: 1.65m^2), weighted for the gender balance in the EXTREME trial (Sacco, 2010). However, as acknowledged by the authors of this study, the H&N patient group was not large enough to allow for generalisation to the whole UK head and neck population.

Furthermore, patients who are the focus of this appraisal, the recurrent/metastatic subgroup of the overall H&N cancer population, are a severely ill group with oral cavity symptoms known to be linked to eating and nutritionally difficulties. Oral cavity patients are typically associated with bulky tumours which impacts on swallowing and is regarded as the most common nutrition-related problem. Once patients have reached the recurrent and/or metastatic phase of the disease they have lost a considerable amount of weight (Vermorken, 2008). As such, it may not be realistic to assume that this population is comparable to the overall patient group. On the basis of these considerations, the mean BSA from the EXTREME trial (1.75m^2), 90% of which were male patients (who are typically heavier than females) was used to populate the updated model. It is worth noting that the ratio of males:females in the overall patient group in the trial (on whom the BSA estimate is based) is greater than this ratio in oral cancer patients in real life. The model therefore overestimates likely average BSA and therefore average cetuximab treatment costs.

The amendment of the BSA parameter necessitated a further adjustment in the model. In the previous submission, NICE accepted a correction for the fact that an assumption that all patients in the stable/response health state will receive cetuximab at 100% of the prescribed dose over estimates the total number of vials of cetuximab received over the lifetime (and therefore the cetuximab costs). The correction was derived by assessing the relationship

between vial use in the EXTREME trial (linked to BSA) and that predicted by the model. This was described in Appendix H5 of the previous submission. The correction estimated the proportion of patients receiving cetuximab at full dose per cycle by counting actual use per cycle in the trial and dividing this by "16 vials for the initial cycle and 13 vials for subsequent cycles". With an update to BSA in the economic model, this correction too must be updated to reflect that at full dose, the average patient (at 1.75m^2) now receives 14 vials (instead of 13) in subsequent cycles (in the model this is cycles 2-6 and 7+). The same methodology was applied as previously, and from the calculated difference in the proportion the following equation was obtained: $y = 0.5946x^2 + 0.3292x$ with x being the proportion of patients in the "stable/response" health state at a certain cycle and y the proportion of patients receiving 16 or 14 vials of cetuximab. This was used to apply a per cycle correction in the model for the predicted number of cetuximab vials.

Assumption 2: Health related QoL- pre-progression utility

The model assumes that treatment-specific utilities apply in the stable disease/response health state (i.e. that cetuximab has some impact on quality of life whilst patients are taking the drug). This assumption was challenged by the ERG (page 55-56 of the ERG report), however we believe it to be clinically justifiable, particularly in the oral cavity patient subgroup and it is supported by:

(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) High best response rates of [redacted] were observed in the oral cavity subgroup in the EXTREME trial. This response to treatment measured by

reduction in tumour size in a population who are associated with bulky tumours will inevitably have a beneficial impact on patients QoL at the pre-progression “stable/ responsive” disease health state.

These two reasons support the use of treatment specific utility values at the stable/response health state.

Assumption 3: Inclusion of a mid-cycle correction

A half cycle correction, as suggested by the ERG (page 38 of the ERG report), has now been implemented in the updated model to ensure that costs and outcomes are not over or under estimated. (ERG, 2008)

Assumption 4: Unit costs updated to 2014/2015 prices

The ERG (page 59) criticised the approach to costing in the previous model which they said came from a mixture of sources using different years. Merck considered that all cost data in the original model is now out of date, and therefore undertook a full update of all cost inputs in the model for the purposes of this resubmission. The codes and references suggested by the ERG (ERG, 2008) in their report in 2008 (page 60-61) have been used to source the updated costs from PSSRU 2015 (PSSRU, 2015) and 2014/2015 NHS reference costs. (NHS, 2014/15) The Electronic Market Information Tool (eMIT) was used to update drug costs as it is believed to most accurately reflect the price at which hospital drugs are purchased (June 2015)[1]. (eMIT, 2015) The table below lists the original and updated costs in the model.

Table 4: Chemotherapy costs per 3-week cycle*

Treatment	Original costs per cycle (source: BNF 55) (£)	Updated costs per cycle (£)	Source
Cetuximab + carboplatin + 5-FU (initial cycle)	[redacted]	[redacted]	eMIT (eMIT, 2015)
Cetuximab + cisplatin + 5-FU (initial cycle)	[redacted]	[redacted]	eMIT (eMIT, 2015)
Cetuximab + carboplatin + 5-FU (cycle 2-6)	[redacted]	[redacted]	eMIT (eMIT, 2015)
Cetuximab + cisplatin + 5-FU (cycle 2-6)	[redacted]	[redacted]	eMIT (eMIT, 2015)
Cetuximab (cycle 7+)	[redacted]	[redacted]	N/A
Carboplatin + 5-FU	712.00	97.35	eMIT (eMIT, 2015)
Cisplatin + 5-FU	292.44	54.55	eMIT (eMIT, 2015)
5-FU	192.00	29.49	eMIT (eMIT, 2015)
Bleomycin	77.80	93.36	BNF 71 (BNF, 2016)
Cisplatin	100.44	25.06	eMIT (eMIT, 2015)
Docetaxel	1,069.50	24.78	eMIT (eMIT, 2015)
Paclitaxel	1,001.72	25.48	eMIT (eMIT, 2015)
Radiotherapy	1,135.93	2,914.12	**2014/15 NHS Reference Costs for Radiotherapy** (NHS, 2014/15) SC28Z: Deliver a fraction of interstitial radiotherapy
Surgery	1,180.66	2,417.68	**2014/15 NHS Reference Costs for Elective Inpatients** (NHS, 2014/15)

Treatment	Original costs per cycle (source: BNF 55) (£)	Updated costs per cycle (£)	Source
			Weighted average of CA83A and CA83B by casemix volume

*Costs of drugs per cycle have been re-estimated using the BSA value of 1.75m2
Radiotherapy costs: 2014/15 NHS Reference Costs for Radiotherapy, SC28Z: Deliver a fraction of interstitial radiotherapy
Surgery cost: 2014/15 NHS Reference Costs for Elective Inpatients, weighted average of CA83A and CA83B by casemix volume

Table 5: Unit costs revisions updated to 2014/2015 prices- hospital and community costs

Item	Previous submission unit cost (£)	Revised unit cost (£)	Source
Inpatient stay in medical oncology ward per day	296.00	362.00	**2014/2015 NHS reference costs for Daycase and regular Day/Night** (NHS, 2014/15) SB15Z: Deliver subsequent elements of a chemotherapy cycle
Outpatient drug administration visit	124.66	204.00	**2014/15 NHS Reference costs for chemotherapy** (NHS, 2014/15) Deliver subsequent elements of a chemotherapy cycle
Consultant Oncologist	87.00	158.00	**2014/15 NHS Reference costs, Consultant Led** (NHS, 2014/15) 370 Medical oncologist (attendance without treatment)
General Practitioner	34.00	44.00	**PSSRU 2015** (PSSRU, 2015)p.177 Per patient contact lasting 11.7 minutes (including carbon emissions (6 KgCO2e)2 (including direct care staff costs, with qualification costs)

Item	Previous submission unit cost (£)	Revised unit cost (£)	Source
Nurse Specialist per hour	38.00	59.00	**PSSRU 2015** (PSSRU, 2015) p.175 advanced nurse (including qualification costs)
CT-scan	77.00	88.05	**2014/15 NHS Reference Costs for Diagnostic Imaging** (NHS, 2014/15) CT Scan of one area - weighted average of RD20A, RD21A and RD22Z by casemix volume
MRI	244.00	137.37	**2014/15 NHS Reference Costs for Diagnostic Imaging** (NHS, 2014/15) MRI scan of one area- weighted average of RD01A, RD02A and RD03Z by casemix volume
Nurse Community	26.00	50.00	**PSSRU 2015** (PSSRU, 2015) p. 169 (including qualification costs)

Table 6: Unit costs revisions updated to 2014/2015 prices- adverse event cost components

Item	Previous submission unit cost (£)	Revised unit cost (£)	Source
Anaemia grade 3	930.04	516.12	**2014/15 NHS Reference Costs for Non-Elective Short Stay** (NHS, 2014/15) Weighted average SA04G, SA04H, J, SA04K and SA04L by casemix volume
Anaemia grade 4	930.04	516.12	**2014/15 NHS Reference Costs for Non-Elective Short Stay** (NHS, 2014/15) Weighted average SA04G, SA04H, J, SA04K and SA04L by casemix volume
Neutropenia grade 3	1.337.42	5,671.50	**2012/13 NHS Reference Costs for Non-Elective Short Stay** (NHS, 2014/15) PA45Z: Febrile Neutropenia with Malignancy inflated by 3.5% to 2014/2015 (OHE,

Item	Previous submission unit cost (£)	Revised unit cost (£)	Source
			2012)
Neutropenia grade 4	1,337.42	5,671.50	**2012/13 NHS Reference Costs for Non-Elective Short Stay** (NHS, 2014/15) PA45Z: Febrile Neutropenia with Malignancy inflated by 3.5% to 2014/2015 (OHE, 2012)
Thrombocytopenia grade 3	84.22	502.63	**2014/15 NHS Reference Costs for Non-Elective Short Stay.** (NHS, 2014/15) Weighted average of SA12G, SA12H, SA12J, SA12k by casemix volume
Thrombocytopenia grade 4	84.22	502.63	**2014/15 NHS Reference Costs for Non-Elective Short Stay.** (NHS, 2014/15) Weighted average of SA12G, SA12H, SA12J, SA12k by casemix volume

Item	Previous submission unit cost (£)	Revised unit cost (£)	Source
Mucositis/ stomatitis/ dysphagia grade 2	94.72	516.13	**2014/15 NHS Reference Costs for Non-Elective Short Stay** (NHS, 2014/15) CB01F: Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0-4
Mucositis/ stomatitis/ dysphagia grade 3	307.18	736	**2014/15 NHS Reference Costs for Non-Elective Short Stay**. (NHS, 2014/15) CB01E: Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 5-8
Mucositis/ stomatitis/ dysphagia grade 4	3,035.70	1,109	**2014/15 NHS Reference Costs for Non-Elective Short Stay**. (NHS, 2014/15) CB01D: Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without

Item	Previous submission unit cost (£)	Revised unit cost (£)	Source
			Interventions, with CC Score 9+
Nausea/ vomiting grade 2	80.68	824.97	**2014/15 NHS Reference Costs for Non-Elective Short Stay** (NHS, 2014/15) FZ13C: Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over
Nausea/ vomiting grade 3/4	333.29	1,484.30	**2014/15 NHS Reference Costs for Non-Elective Short Stay** (NHS, 2014/15) Weighted average of FZ27F and FZ27G by casemix volume
Nausea/ vomiting grade 4	1,099.06	2, 038.09	**2014/15 NHS Reference Costs for Non-Elective Short Stay.** (NHS, 2014/15) FZ27E: Intermediate Therapeutic General Abdominal Procedures, 19 years and over, with

Item	Previous submission unit cost (£)	Revised unit cost (£)	Source
			CC Score 3+
Pyrexia grade 3 or 4	1.103.37	2,661.41	**2014/15 NHS Reference Costs for Non-Elective Short Stay** (NHS, 2014/15) WJ02B: Major Infectious Diseases with Single Intervention
Acne/ rash grade 3 or 4	43.38	36.10	**eMIT and BNF 71** (eMIT, 2015) (BNF, 2016) 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)

Assumption 5: Extrapolation of life years gained

One of the criticisms from the ERG in our previous submission, was that the model may have overestimated the benefit provided by cetuximab (page 53-53 of ERG report). Since the original submission, 5 year follow-up data of the EXTREME study has become available and in fact, the outcomes from this update are generally more favourable for cetuximab in years 2-5 than predicted by the model (Figure 5). (Vermorken, 2014) To test the parametric model used to predict overall survival in our original model, we selected random time points between 24 and 60 months and compared actual survival to predicted (Table 7). While we recognize that post 24 months the model underestimates survival in both treatment arms importantly, there is a considerable underestimate in the incremental survival benefit and therefore, the benefits of cetuximab are unlikely to be fully realised in our current model.

Merck acknowledge that the comments above relate to the overall population, however there is no reason to expect this pattern to be different in the oral cavity subgroup.

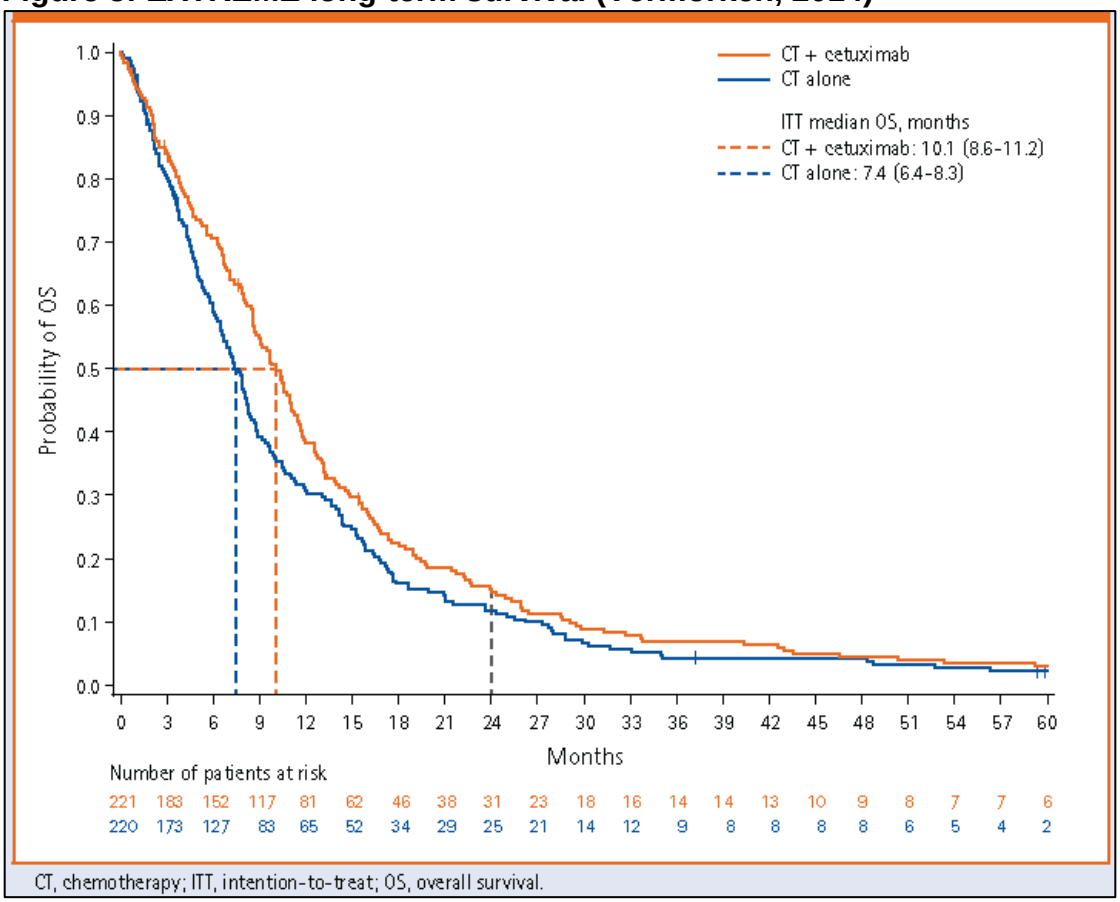
Table 7: Overall survival at random time points from the model and 5 year trial data

Treatment arm	% of patients alive at 28 months (1376 days)		% of patients alive at 36 months (1769 days)		% of patients alive at 42 months (2064 days)		% of patients alive at 59.5 months (2924 days)	
	Trial	Model	Trial	Model	Trial	Model	Trial	Model
Cetuximab	11.7	0.8	7.1	0.1	6.5	0.02	2.9	0
Standard of care	8.3	0.08	4.4	0.01	4.4	0.002	1.7	0
Increment	**3.4**	**0.72**	**2.7**	**0.09**	**2.1**	**0.018**	**1.2**	**0**

The timeframe for this re-submission and the specification not to incorporate new clinical data in the model has meant that Merck has not fully utilised the updated EXTREME data. However, it has proved useful in confirming that whilst projections of OS in the model don't match perfectly the longer term data, this is in a direction that is conservative and biases against cetuximab. While it is difficult to quantify precisely the impact that extended survival

benefit observed in the 5-year data may have, the improvement in overall survival is likely to have a positive impact on the [redacted].

Figure 5: EXTREME long-term survival (Vermorken, 2014)



CT, chemotherapy; ITT, intention-to-treat; OS, overall survival.

3.2 If the population to whom the patient access scheme/ commercial access agreement applies (as described in sections 3.4 and 3.5) is not the same as that in the published technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access

scheme/ commercial access agreement. You must also complete the rest of this template.

Not applicable, the patient access scheme applies to all uses of cetuximab.

3.3 Please provide a summary of the clinical effectiveness parameters (resulting from the Committee's preferred evidence synthesis) which are used in the economic model which includes the patient access scheme/ commercial access agreement.

Table 8: Clinical effectiveness parameters for the oral cavity subgroup

	CTX (n=19)	**Cetuximab & CTX (n=21)**	**HR (95% CI interval**
Progression Free Survival (PFS)	2.8	6.1	0.34 (0.21–0.55)
Overall Survival (OS)	4.4	11.0	0.42 (0.26–0.67)
Utility at stable/ response disease*	0.69	0.65	NR
Utility at progressive disease	0.52	0.52	NR

*The utility scores for the oral cavity subgroup were assumed to be the same as those for all RM SCCHN tumour locations

The table above shows the clinical effectiveness parameters in the economic model for the oral cavity subgroup. No changes to efficacy inputs have been made from the previous submission.

3.4 Please list any costs associated with the implementation and operation of the patient access scheme/ commercial access agreement (for example, additional pharmacy time for stock management or rebate calculations). Please give the reference source of these costs. Please provide sufficient detail to allow the replication of changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. Please refer to section 6.5 of the 'Specification for company submission of evidence'.

Not applicable, this is a simple patient access scheme with no costs associated with implementation and operation of the scheme

3.5 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme/ commercial access agreement. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable, this is a simple patient access scheme with no additional treatment related costs incurred by implementing the patient access scheme.

Summary results

New base-case analysis

3.6 Please present in separate tables the cost-effectiveness results as follows.[2]

- the results for the intervention without any (new) patient access scheme/ commercial access agreement; that is with the price for the technology considered in the published guidance.
- the results for the intervention with the patient access scheme/ commercial access agreement.

The table below provides the costs and ICER at the previous cetuximab price to the NHS of £136.50 per vial (i.e. this reflects the price that the NHS is currently paying for cetuximab), taking into account the new assumptions imposed in the model.

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

Table 9: New base-case cost-effectiveness results using the price as in the published technology appraisal: Oral cavity subgroup

	Cetuximab and/or carboplatin/ cisplatin plus 5-FU	Carboplatin/ Cisplatin plus 5-FU (standard of care)
Intervention cost (£)	[redacted]	703
Costs due to treatment related resource use (£)	[redacted]	6,340
Treatment independent costs (dependent on disease state, £)	[redacted]	2,916
AE costs (£)	[redacted]	2,310
Total costs (£)*	[redacted]	10,299
Difference in total costs (£)	N/A	[redacted]
LYG	1.13	0.58
LYG difference	N/A	0.55
QALYs	0.67	0.32
QALY difference	N/A	0.35
ICER (£)	N/A	[redacted]

*Half cycle correction applied to total costs
ICER value includes BSA of 1.75m^2, treatment specific utility, HCC to costs and benefits and 2014/2015 costs
AE: adverse event; LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 10 below presents the ICER for the oral cavity subgroup at the new cetuximab price of [redacted] (implementing the revised patient access scheme which is a [redacted] from cetuximab's list price) [redacted] than the ICER at the previous price.

Table 10: New base-case cost-effectiveness results using the patient access scheme/ commercial access agreement- Oral cavity subgroup

	Cetuximab and/or carboplatin/ cisplatin plus 5-FU	Carboplatin/ Cisplatin plus 5-FU (standard of care)
Intervention cost (£)	[redacted]	703
Costs due to treatment related resource use (£)	[redacted]	6,340
Treatment independent costs (dependent on disease state, £)	[redacted]	2,916
AE costs (£)	[redacted]	2,310
Total costs (£)*	[redacted]	10,299
Difference in total costs (£)	N/A	[redacted]
LYG	1.13	0.58
LYG difference	N/A	0.55
QALYs	0.67	0.32
QALY difference	N/A	0.35
ICER (£)	N/A	[redacted]

* Half cycle correction applied to total costs
ICER value includes a BSA of 1.75m^2, treatment specific utility, HCC to costs and benefits and 2014/2015 costs
AE: adverse event; LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

3.7 Please present in separate tables the incremental results as follows. [3]

- the results for the intervention without the (new) patient access scheme/ commercial access agreement, that is with the price for the technology considered in the published appraisal.
- the results for the intervention with the patient access scheme/ commercial access agreement.

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

[3] For outcome-based schemes, please see section 5.3.9 in appendix 5.3.

Not applicable. Only one intervention and one standard of care is included in the model. The costs and ICER is presented above.

Sensitivity analyses with the relevant PAS/CAA

3.8 Please refer to the published guidance to identify the key sensitivity and scenario analyses (that is, analyses that were discussed in the 'considerations' section and which alter the ICER). Present the results of these sensitivity and scenario analyses with the patient access scheme/ commercial access agreement.

Considerations mentioned in section 4 of NICE's guidance and alternative assumptions and parameters explored by the ERG that have not been included in the base case above have been used to inform a number of scenario analyses (Table 11).

Table 11: Scenario analysis informed by considerations highlighted by the previous CommitteeNICE guidance considerations

Parameter	Assumption in updated model	Scenario analysis assumption
Body surface area	BSA of 1.75m^2 used to calculate treatment dosing Worksheet "Unit costs"- Drug acquisition costs and Surgery and Radiation costs table	**Scenario 1:** ERG's recommended BSA of 1.83m^2 based on results of a UK audit study in general head and neck patients, weighted for the gender balance in the EXTREME trial.
Equivalent utility in pre-progression health state across both treatment arms	Treatment specific utility (0.69 for cetuximab and 0.65 for standard of care) pre-progression and at stable disease Worksheet "Model Parameters" worksheet cells C7:8	**Scenario 2:** The same mean utility for both treatment arms (0.65) in the pre-progression health state
Frequency of cetuximab administrations	Cetuximab doses are given weekly through treatment duration	**Scenario 3:** [redacted] *See explanation below*

Scenario 3: Cetuximab administration in the real world clinical setting

Through our interactions with healthcare professionals and our own market research we have identified that cetuximab is not always administered as weekly infusions to SCCHN patients. [redacted]

(worksheet “Resource use and Cost” cells F41:43).

The three scenarios listed above have been run in the updated economic model separately using the new patient access scheme price, inclusion of half cycle correction and 2014/15 prices. The resulting ICERs are presented in the tables below. Assuming that the QoL in the pre-progression health state is the same between the intervention and comparator arm has the biggest impact on the ICER increasing it by £2,883 from the base case ICER value. However, if we are to take into account how cetuximab is used in the real world and that not all patients receive weekly infusions, the ICER decreases by £5,895 to [redacted] making cetuximab a cost-effective treatment in a high need patient group (Figure 13 and Figure 14).

Table 12: Scenario analysis 1: BSA of 1.83m^2

	Cetuximab and/or carboplatin/ cisplatin plus 5-FU	Carboplatin/ Cisplatin plus 5-FU (standard of care)
Intervention cost (£)	[redacted]	703
Costs due to treatment related resource use (£)	[redacted]	6,340
Treatment independent costs (dependent on disease state, £)	[redacted]	2,916
AE costs (£)	[redacted]	2,310
Total costs (£)*	[redacted]	10,299
Difference in total costs (£)	N/A	[redacted]
LYG	0.67	0.32
LYG difference	N/A	0.55
QALYs	1.13	0.58
QALY difference	N/A	0.35
ICER (£)	N/A	[redacted]

*Half cycle correction applied to total costs
ICER value includes the change in price as per the new patient access scheme, HCC, treatment specific pre-progression utility and 2014/15 unit costs
AE: adverse event; LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 13: Scenario analysis 2: equivalent utility estimates across both treatment arms

	Cetuximab and/or carboplatin/ cisplatin plus 5-FU	Carboplatin/ Cisplatin plus 5-FU (standard of care)
Intervention cost (£)	[redacted]	703
Costs due to treatment related resource use (£)	[redacted]	6,340
Treatment independent costs (dependent on disease state, £)	[redacted]	2,916
AE costs (£)	[redacted]	2,310
Total costs (£)*	[redacted]	10,299
Difference in total costs (£)	N/A	[redacted]
LYG	1.13	0.58
LYG difference	N/A	0.55
QALYs	0.66	0.32
QALY difference	N/A	0.34
ICER (£)*	N/A	[redacted]

*Half cycle correction applied to total costs
ICER value includes the change in price as per the new patient access scheme, HCC, BSA of 1.75m^2 and 2014/15 unit costs
AE: adverse event; LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 14: Scenario analysis 3: Frequency of cetuximab administrations

	Cetuximab and/or carboplatin/ cisplatin plus 5-FU	Carboplatin/ Cisplatin plus 5-FU (standard of care)
Intervention cost (£)	[redacted]	703
Costs due to treatment related resource use (£)	[redacted]	6,340
Treatment independent costs (dependent on disease state, £)	[redacted]	2,916
AE costs (£)	[redacted]	2,310
Total costs (£)*	[redacted]	10,299
Difference in total costs (£)	N/A	[redacted]
LYG	1.13	0.58
LYG difference	N/A	0.55
QALYs	0.67	0.32
QALY difference	N/A	0.35
ICER (£)	N/A	[redacted]

*Half cycle correction applied to total costs
ICER value includes the change in price as per the new patient access scheme, BSA of 1.75m^2, HCC, treatment specific pre-progression utility and 2014/15 unit costs
AE: adverse event; LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

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

The PSA graphs and CEAC curves are presented below for the base case, scenario 1, scenario 2 and scenario 3.

Figure 6: Cost-utility plane- Base case

Figure 7: CEAC curve- Base case

Figure 8: Difference in distribution of health states over time between patients treated with cetuximab and patients not treated with cetuximb-base-case

Figure 9: Cost-utility plane- Scenario 1, BSA of 1.83m^2

Figure 10: CEAC curve- Scenario 1, BSA of 1.83m^2

Figure 11: Cost-utility plane- Scenario 2, equivalent utility estimates across both treatment groups

Figure 12: CEAC curve- Scenario 2, equivalent utility estimates across both treatment groups

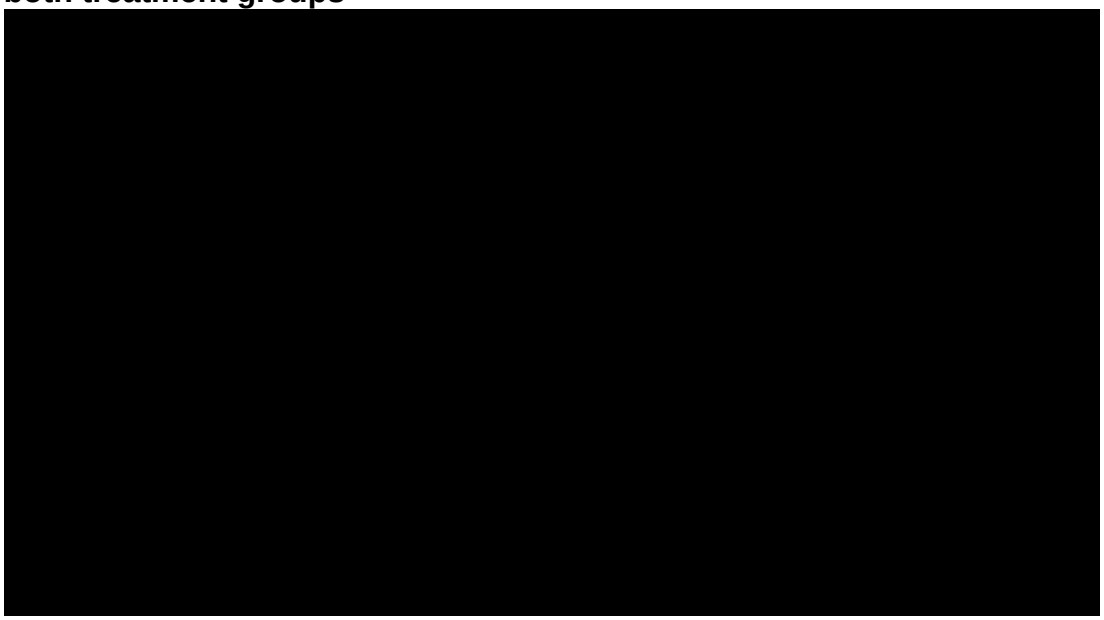


Figure 13: Cost-utility plane- Scenario 3, frequency of cetuximab administrations

Figure 14: CEAC curve- Scenario 3, frequency of cetuximab administrations

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

Not applicable

4 Conclusion

Cetuximab is a clinically effective treatment for all patients with head and neck cancer. Clinical evidence suggests that efficacy is even greater in patients with tumours of the oral cavity.

A number of criticisms from the last submission have been addressed and an updated model with current costs has been presented demonstrating a new base case ICER of [redacted] for the oral cavity subgroup. There are a number of reasons why Merck believe that this ICER underestimates the true value of cetuximab to the NHS and is an overestimate of the true costs. When considering the five year survival data from the EXTREME trial, it is clear that the model underestimates the incremental overall survival benefit of cetuximab versus standard of care. Beyond two years, patients are actually living for longer after treatment with cetuximab than estimated by the model which assumes that all patients have died by year 3. Whilst the same is true of the comparator arm in the model, i.e. overall survival benefit is also underestimated in the model, this is not to the same degree. The underestimate of benefit will be greater than any underestimate of cost because at these points in the model, patients are likely to have progressed and the weekly treatment costs associated with cetuximab will no longer be accruing.

In the context of end of life treatment, the EXTREME trial shows that patients with an oral cavity tumour show both a significant incremental delay in progression (median PFS of 3.3 months) and incremental improvement in overall survival (median OS of 6.6 months) beyond the 3 months required to meet the criteria. For patients who have an extremely low expected survival of around 4 months this is a considerable difference.

Merck have previously argued the position that in the context of established treatment paradigms, the economic model should reflect the true costs of delivery of treatments to the NHS. As is the case with metastatic colorectal cancer, cetuximab is not administered solely on a weekly basis in the NHS for patients. When real life data on the frequency of cetuximab administration was

included in the model (scenario analysis 3), cetuximab was found to be cost effective in the oral cavity subgroup [redacted].

Given the poor prognosis of RM SCCHN patients with oral cavity tumour, their notable beneficial response to treatment and the economic evidence presented above, we urge the Committee to allow patients to continue benefitting from cetuximab treatment.

5 Additional documents

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

Not applicable

5.2 Details of outcome-based schemes

Section not applicable

6 References

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Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

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

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] RCP registrar, submitting on behalf of:

Name of your organisation: NCRI-RCP-RCR-ACP

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

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

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Cetuximab in combination with cisplatin/carboplatin based chemotherapy is used routinely in the UK (funded through CDF) for patients with recurrent/metastatic HNSCC who are fit enough for the combination and who have no contraindications to any of the component therapies. The treatment applies to all subgoups of Head and Neck Squamous Carcinoma (HNSCC), including both HPV +ve and –ve disease and is delivered as day-case treatment through cancer centres and units.

As the only therapy to date that has shown a meaningful prolongation in overall survival in this group of patients, it is considered the gold-standard therapy for this population of patients, and is almost always the comparator arm in trials in first-line metastatic disease. This is exampled by its inclusion within the European Head & Neck Treatment Guidelines (Annals of Oncology 2010; 21 (Supp 5) v184-186) and the NCCN Head and Neck Cancer Guidelines (2013).

There are no major differences of opinion in this regard, although uptake may differ between oncologists, partly relating to assessment of fitness. There may be variations in use across the country relating to socioeconomic status and thus proportions of patients presenting late and/or with significant comorbidity.

Patients who are not fit enough for cetuximab combination therapy are likely to be treated with single agent chemotherapy or best supportive care only.

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CDF Rapid reconsideration process

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

Occasionally patients who do not want to travel to hospital for weekly therapy may receive cisplatin/carboplatin and 5FU without the cetuximab.

Treatment occurs within its licence (through the CDF).

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

As this technology has been funded through the CDF for several years, there are no practical barriers to use. Most institutions (and clinical teams) have extensive experience with the use of cetuximab in this and other indications. Although slightly more challenging to use than cisplatin/carboplatin & 5FU alone (which would be the main alternative treatment), cetuximab-related side effects are usually very manageable and in the main toxicity and contraindications are related to the platinum component of the combination.

The chemotherapy backbone is delivered 3 weekly whereas the cetuximab is delivered as a short weekly infusion and therefore does require additional visits to the hospital and associated time in chemotherapy day care units.

The cetuximab is effectively delivered in two phases, initially in combination with the chemotherapy for 4-6 3-weekly cycles and then, for patients whose disease remains controlled, as maintenance therapy until progression.

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CDF Rapid reconsideration process

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Patient selection is primarily clinical, with performance status being the most important factor for consideration. Assessment of renal function, hearing etc are required for the cisplatin element of the combination. Discontinuation of treatment would be due to the occurrence of intolerable toxicity or progression; which would be monitored in a similar manner to chemotherapy alone.

There is no suggestion that the experience of the use of the technology since license is meaningfully different from the clinical trial data (EXTREME trial), which lead to its license, and it remains the global gold-standard.

The EXTREME trial was performed in similar patient groups including in Europe (and UK). While a select group (performance status etc), this has generally been reflected in practice as well, and the results from the EXTREME trial are likely to be relevant to the UK population.

The EXTREME trial showed a clinically significant improvement in survival. This is particularly important in this group of patients who have a very poor survival in the absence of treatment.

Adverse reactions to cetuximab are similar to those described in the EXTREME trial and other trials of this agent, with no significant emergent side effects subsequently. A quality of life analysis of the EXTREME trial did not show significant differences with the addition of cetuximab. The acneiform rash is generally tolerable, and may ameliorate with time. However, in clinical practice possibly higher numbers of patients discontinue due to toxicity (including relatively low grade but persistent toxicity) than in trials.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Cetuximab is already in widespread use and has been available in this setting via the CDF and so there will be no impact on current services.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

None

NHS E submission to NICE re-appraisal of cetuximab in combination with 1st line chemotherapy in advanced/metastatic head and neck cancer

1. The CDF re-considered in August 2015 the clinical benefit of cetuximab as part of 1st line platinum-based combination chemotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck.
2. The main evidence base was centred on a prospectively performed trial which had randomised patients with recurrent or metastatic squamous cell head and neck cancer to cetuximab plus a 1st line platinum-based combination of 5-fluorouracil and cisplatin/carboplatin vs the same chemotherapy alone. This trial had been published in 2008 and the primary endpoint was overall survival. There were 442 patients in the study and the median duration of follow up was at least 18 months. The addition of cetuximab resulted in significant improvements in progression-free survival [PFS] (5.6 vs 3.3 mo, Δ 2.3 mo, hazard ratio [HR] 0.54, 95% confidence intervals [CI] 0.43-0.67, p <0.001) and overall survival [OS] (10.1 vs 7.4 mo, Δ 2.7 mo, HR 0.80, 95% CI 0.64-0.99, p=0.04], respectively.
3. Quality of life (QOL) data using the EORTC QLQ-C30 questionnaire and the QLQ Head and Neck 35 module had been collected and published for this trial. For the QLQ-C30, cycle 3 and month 6 mean scores for cetuximab plus chemotherapy were not significantly worse than for chemotherapy alone. For the QLQ-H&N35 module, the mean score for the cetuximab arm was not significantly worse than that for the chemotherapy arm for all symptom scales at all post-baseline visits.
4. Although grade 3 and 4 adverse events were slightly greater with the addition of cetuximab (82% vs 76%), there was significantly increased sepsis and skin reactions with cetuximab plus chemotherapy. The median duration of treatment with cetuximab was 4.2 mo.
5. The CDF noted that neither the degree of EGFR expression nor the tumour EGFR copy number were predictive for any survival benefit with cetuximab.
6. The CDF recognised that there were other systemic therapies available in head and neck cancer. The CDF also noted the fact that there had been little improvement in the systemic therapy of recurrent/metastatic squamous cell head and neck cancer for many years. It did not regard the benefits of cetuximab in this indication to be a step change in the management of head and neck cancer cancer when considering the small survival benefit, the hazard ratio which only just attained statistical significance and the absence of any robustly determined differential tail in the OS curve over time.
7. NHS England remains aware of the national support for the use of cetuximab in this indication as evidenced by the continued number of applications to the CDF for use within this cohort.
8. NHSE notes that NICE is currently re-appraising cetuximab in the management of advanced/metastatic colorectal cancer as part of the transition from the previous CDF to consideration of baseline commissioning or not.

9. NHSE also notes that NICE is due to appraise nivolumab as 2nd line treatment of advanced/metastatic head and neck cancer but the outcome of this nivolumab appraisal will not affect the current patient pathway as it is for 2nd line therapy.
10. In summary, NHSE notes that cetuximab when combined with 1st line platinum-based combination chemotherapy offers modest clinical benefit at the expense of acceptable toxicity and without impairing quality of life. Patients and clinicians are keen to retain cetuximab as part of 1st line chemotherapy. The key issue lies in consideration of its cost effectiveness.

[redacted]

[redacted]

September 2016

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) [ID1016]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **NCRI-ACP-RCP-RCR** and consequently I will not be submitting a personal statement.

Name: .....

Signed: .....

Date: 11/01/2016

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) [ID1016]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **NCRI-ACP-RCP-RCR** and consequently I will not be submitting a personal statement.

Name: [redacted]

Signed: [redacted]

Date: .14/09/2016

ERG REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Head and neck cancer (squamous cell carcinoma) – cetuximab (review of TA 172) [ID1016]

CDF rapid reconsideration

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 08/206/01

Completed 01 September, 2016

CONTAINS CIC

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 the use of cetuximab (Erbitux®) for the treatment of recurrent/metastatic head and neck cancer. The original Single Technology Appraisal (STA) was conducted in 2008. The final NICE guidance was issued in April 2009 and did not recommend the use of cetuximab in this patient population.

1.1 Context and approach to rapid reconsideration

To allow these rapid reconsideration exercises to proceed with the minimum risk of delay, the expected procedures have been restricted in scope for the company making a resubmission and for the Evidence Review Group (ERG) who is 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.

2 SPECIFIC DETAILS OF THIS RAPID RECONSIDERATION

2.1 Considerations from existing guidance and new CS

As with the original submission the primary data considered in the CS comes from the EXTREME trial.[1] Details of the trial characteristics are presented in Table 1

Table 1 EXTREME trial characteristics

Design	Intervention	Inclusion criteria (main)	Exclusion criteria (main)	Outcomes
Multicentre, European phase III open label Patients (n=442) Randomisation 1:1 ratio Stratification according to receipt or non-receipt of previous CTX and KPS score	Cetuximab plus CTX (cisplatin plus 5-FU or carboplatin plus 5-FU) n=222 CTX n=220 Oral cavity patients Cetuximab plus CTX 46/222 (21%) CTX 42/220 (19%)	18 years +; Histologically or cytologically confirmed recurrent and/or metastatic SCCHN; ineligibility for local therapy; At least one lesion bio-dimensionally measurable; KPS ≥70; Adequate hematologic, renal, hepatic function; Tumour tissue available for evaluation of EGFR expression	Surgery or irradiation within the previous 4 weeks; Previous systemic CTX unless part of multimodal treatment for locally advanced disease completed > 6 months before study entry; Nasopharyngeal carcinoma; Concomitant anticancer therapies	Primary: OS (time from randomisation to death) Secondary : PFS (time from randomisation to radiologic confirmation of disease progression, or death from any cause within 60 days after the last assessment or randomisation, whichever came first); A variety of response rates; Quality of life

CTX=chemotherapy treatment; OS= overall survival; PFS = progression free survival; TTF = time to treatment failure; SCCHN=squamous cell carcinoma of the head and neck; KPS=Karnofsky performance status; EGFR=epidermal growth factor receptor

It is worth noting the clinical issues addressed as part of the Appraisal Committee (AC) discussion and included in the existing guidance[2] that are addressed as part of the CS that has been received. These include limiting consideration to the subgroup of patients with oral cavity carcinoma and a case for end of life criteria and are outlined in Table 1

The CS makes reference to more up-to-date five year survival data available from the EXTREME trial and presented as an abstract in 2014.[3] This data is for the whole population of the EXTREME trial and does not provide any data related to the specific sub group of patients with oral cavity carcinoma.

Table 2 Considerations in existing guidance and CS

NICE guidance[2]	Company position[4]	Evidence in CS for this position
Subgroup – oral cavity Clinical specialists informed the AC; 'that patients with tumours in the oral cavity have a relatively favourable prognosis compared with the average prognosis for recurrent and/or metastatic SCCHN. (page 13) 'The Committee accepted that the trial demonstrated the efficacy of cetuximab plus platinum-based chemotherapy in patients with recurrent and/or metastatic SCCHN, but it was not persuaded that the evidence supported using the subgroup estimate for clinical effectiveness in the economic model.' (page 14)	The CS also makes a case for the poor prognosis for this patient population. CS states that they focused on the oral cavity subgroup because 'there is little chance of becoming cost effective in the overall population' page 12	Combined data from two RCTS of patients (n-399) with recurrent head and neck cancer treated with cisplatin-based combination chemotherapy[5] 'median survival in patients with oral cavity or hypopharyngeal cancers was 0.52 years compared to 0.70 years in patients with other head and neck cancers (p=0.04)' page 9 of CS Reference to clinical expert testimony – data held by the company and not available to the ERG
End of life consideration 'The Committee considered the criteria only in relation to the estimate of overall survival for the cohort population because it did not consider the subgroup data to be robust' (page 16) The committee considered that the life expectancy for these patients was likely less than 24 months. However, 'it was also aware that the predicted life years gained from the economic modelling for this group was 0.187, reflecting a gain in overall survival of approximately 2.2 months. The Committee therefore did not consider that this estimate of gain in overall survival was in keeping with the criteria relating to extension of life' (pages 16-17)	Outcomes demonstrate end of life benefit shown in EXTREME trial data	Data from EXTREME[1] 'In the context of end of life treatment, the EXTREME trial shows that patients with an oral cavity tumour show both a significant incremental delay in progression (median PFS of 3.3 months) and incremental improvement in overall survival (median OS of 6.6 months) beyond the 3 months required to meet the criteria.' (page 59) Life years gained for oral cavity patients (Table10 – page 47) 1.13 years for Cetuximab plus CTX versus 0.58 years for CTX patients Additional data from a single arm trial of patients (n=54) that received combination treatment and reported median OS of 14 months.[6]

2.2 Cetuximab drug costs

The company proposes a new cetuximab price of [redacted], which incorporates a revised patient access scheme (PAS). The company states that this new price represents a [redacted] from cetuximab's list price (£178.10/20ml [100mg vial] and £795.10/100ml [500mg vial]). However, the previous acquisition cost to the NHS was £136.50/20ml and £682.50/100ml vial by means of a procurement discount.

It is worth noting that '[redacted]'(page 21)

3 MODEL ALTERATIONS

The CS is based on a modified version of the decision model used in the original technology appraisal (TA172), with amendments to address some of the issues highlighted by the ERG in their 2008 report and specifically mentioned by the Appraisal Committee in Section 3.15 of the ACD.[7]

- the absence of a mid-cycle correction
- restricting analysis to the 24 months period of available follow-up data
- combining mean utility estimates across treatment arms
- using UK audit data for mean body-surface area (BSA) for calculating drug costs
- using a recent common price base for all hospital and care costs

3.1 Implementing ERG recommended amendments

3.1.1 Continuity correction

Ideally a decision model should be able to accommodate accurately events occurring at any time following randomization. However, in practise this leads to very large and unwieldy models depending on the degree of precision required (daily/hourly/other). The compromise generally used involves dividing time into discrete segments and then updating all variables and results at each discrete time point. Inevitably this provides only an approximation to the true costs and outcomes of any treatment as important changes can take place at any time between the chosen model discrete times. To compensate for this imprecision it is common practice to introduce a 'continuity correction' to smooth the effects of changes occurring between modelled time points.

The original version of the company model did not include any such continuity corrections. The ERG recommended in 2008 the use of 'mid-cycle' corrections which involve estimating both costs and outcomes across each time period in the model by averaging the determining variable (e.g. patients alive, patients on treatment, etc.) across the start and end points of each period. In their revised model the company have chosen not to use such a mid-cycle correction, but have instead applied a simpler 'half-cycle correction' which applies a single alteration to each estimated model output based on only the first and last time point covered by the model. The 'half-cycle correction' is necessarily less accurate than the 'mid-cycle' correction method since it does not follow the time-varying pattern of each model variable across many years, and therefore fails to reflect accurately the effect of discounting both cost and outcome results over the duration of the assessment.

The ERG has investigated the differential effects of these two methods on some of the variables in the current version of the company model, and concluded that although there is evidence of differences, these are relatively minor compared with other issues identified below, and therefore do not warrant further attention.

3.1.2 Limited model duration

The original company model projected the then available clinical evidence (a maximum of 24 months follow-up) for a lifetime in accordance with the NICE scope. However, the AC were concerned that extrapolation of limited short-term follow-up trends over extended periods may lead to unreliable cost-effectiveness estimates.

The current company model is calibrated using extended 5-year follow-up data, so that in part uncertainties evident to the AC previously in this regard no longer apply.

3.1.3 Pre-progression utility estimates

The utility value applied to time spent with stable disease or with response to treatment prior to disease progression is a critical model variable, as the majority of patient survival benefit seen in the EXTREME trial occurred prior to disease progression.

No utility data were collected in the EXTREME trial. The EORTC quality of life survey was used in the trial but response rates were generally poor. A published algorithm was used to estimate UK-equivalent EQ-5D utility estimates from the available EORTC survey data. The uncertainty (confidence interval) for these estimates is very wide, so that the observed differences in mean utility estimates for patients either before or after disease progression are not statistically significant. Both the company and the ERG agreed that a single overall utility estimate is appropriate for the post-progression health state. However, the company

argue that separate treatment-specific utility estimates should be used pre-progression on two grounds:

- that there are better response rates for cetuximab than for the comparator
- that cetuximab has a better adverse event profile

The ERG presented evidence to suggest that any utility differences attributable to adverse events would be very small, and inconsequential compared to the difference claimed for cetuximab.

It is also worth pointing out that the difference in pre-progression utility estimates is reduced but not eliminated in the corresponding post-progression utility estimates where differences in pre-progression response rates and adverse events largely lose relevance. This suggests that the treatment-specific non-significant utility differences in the trial data are simply explained as random effects of case-mix variation.

3.1.4 Estimating drug costs

The company has not altered its method of estimating the acquisition cost of drugs (including cetuximab), relying on the mean BSA value recorded in the EXTREME trial and making no adjustment for the gender differences in BSA and other body metrics observed in general population surveys, and in the published UK audit study cited by the ERG (Sacco, et al[8]). The company method of costing does not take any account of the variation in BSA within the treated population. The company suggests that the BSA seen in the specific trial population will not correspond to the BSA distribution in the wider head & neck cancer UK population.

3.1.5 Price base for hospital and care costs

The company has updated all relevant costs and prices to a common 2014/15 price base.

3.2 ERG analysis and amendments

The ERG submitted a set of clarification requests to NICE for the company to provide important information specific to the Oral Cavity subgroup of the EXTREME clinical trial. In particular, these included full Kaplan-Meier (K-M) analysis results showing K-M survival estimates at each event time, for both treatment arms in the EXTREME trial for overall survival, and progression-free survival using the most recent data cut and based on the investigator assessment of disease progression. These requests were aimed at validating the company approach to modelling survival outcomes, and if necessary allowing alternative interpretations of the trial evidence to be assessed.

3.2.1 Progression-free survival

Analysis by the ERG of the latest EXTREME trial PFS K-M data suggested that the simplest and most accurate representation of the data in both trial arms is to assume a constant progression hazard over time (i.e. a straight-line trend for the cumulative hazard plot in Figure 1. This is in contrast to the company's use of Weibull functions for both trial arms which show a consistent bias towards over-estimating PFS for both treatment arms (Figure 2).

In order to recognise the primacy of original trial data over any modelled projection, the ERG has chosen to use the EXTREME trial K-M data directly in the model, and only apply the modelling projection at the end of the available trial data (after 13 months for the Cetuximab + CTX arm, and after 6 months for the CTX only arm.

The ERG method of modelling lifetime PFS results in a slightly increased mean estimated PFS net gain in mean PFS of 4.09 months (Table 3), and a reduction of £1,067 per QALY gained from the base case estimated deterministic ICER.

Table 3 Comparison of PFS estimates using company and ERG methods

Estimation method	Cetuximab+CTX (months)	CTX only (months)	PFS gain (months)
Company base case	7.52	3.49	+ 4.03
ERG PFS analysis	7.31	3.22	+ 4.09

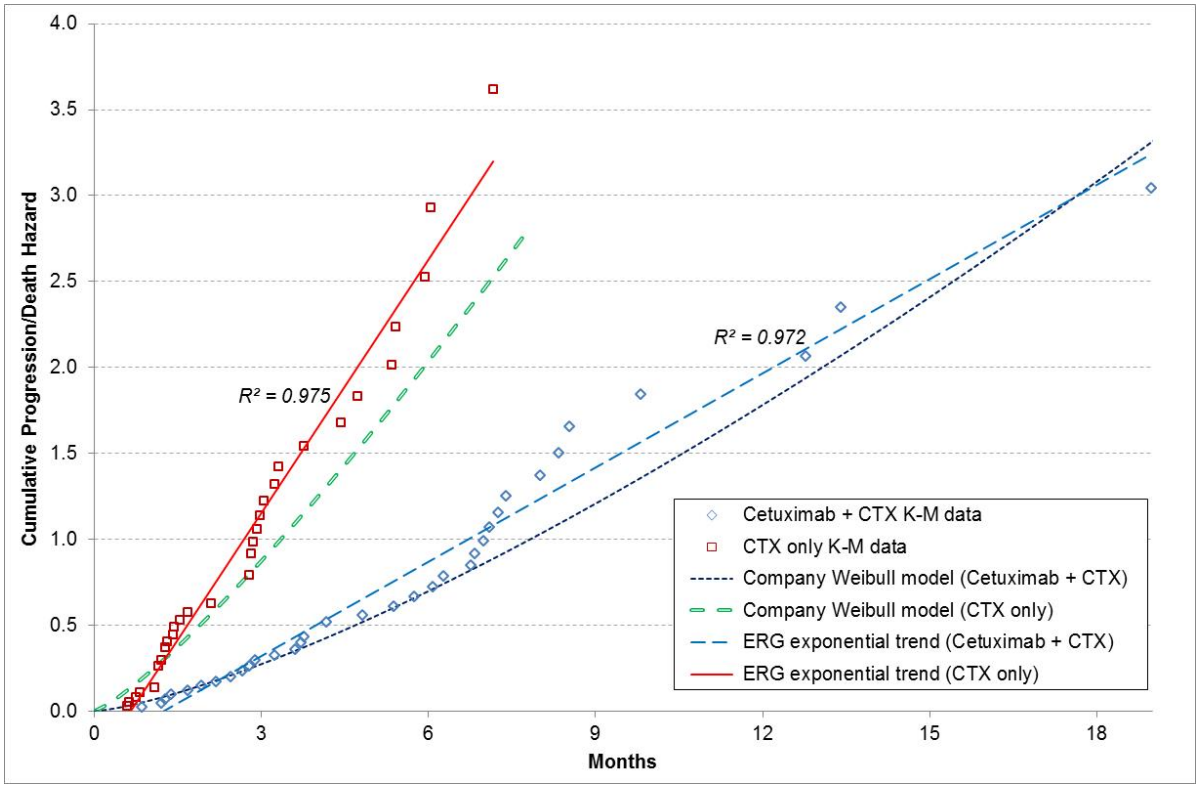

Figure 1 Comparison of Company and ERG modelling of PFS cumulative hazard

CTX = chemotherapy; K-M = Kaplan-Meier analysis

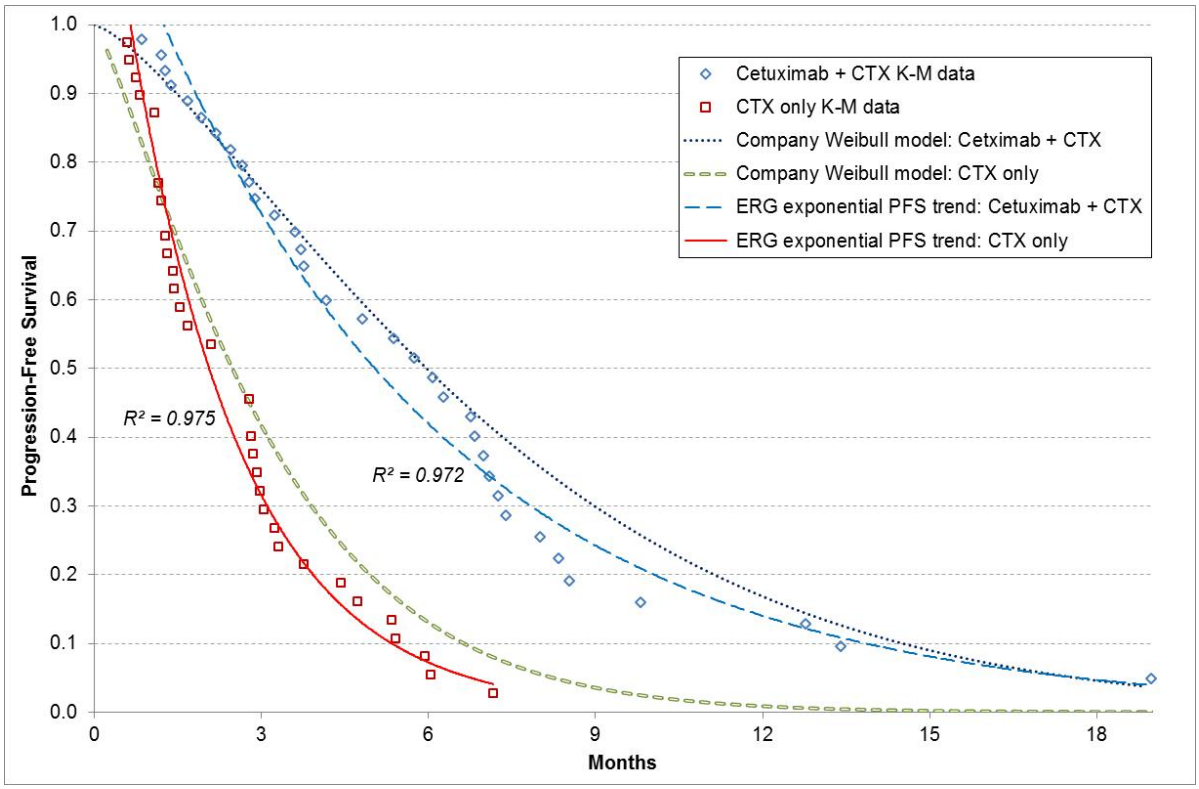

Figure 2 Comparison of Company and ERG modelling of PFS

CTX = chemotherapy; K-M = Kaplan-Meier analysis

3.2.2 Overall survival

Analysis by the ERG of the latest EXTREME trial OS K-M data suggested a different pattern of temporal trends for OS. At 7-8 months there is evidence of the establishment of similar constant progression hazard trends over time (i.e. straight-line long-term trends in the cumulative hazard plot in Figure 3). This is in contrast to the company's use of Weibull functions for both trial arms; in particular, there is a substantial deviation from trial data in the comparator arm after about 5 months.

Figure 4 and Table 4 show that the ERG alternative approach to reflecting the long term survival of patients in the oral cavity subgroup, results in slightly reduced survival in the Cetuximab+CTX arm and a small improvement in OS for the CTX arm, so that the OS gain attributable to cetuximab is reduced from 6.72 months to 6.40 months. This has the effect of increasing the estimated deterministic ICER by £1,492 per QALY gained

Table 4 Comparison of OS estimates using company and ERG methods

Estimation method	Cetuximab+CTX (months)	CTX only (months)	OS gain (months)
Company base case	13.68	6.95	+ 6.72
ERG OS analysis	13.51	7.12	+ 6.40

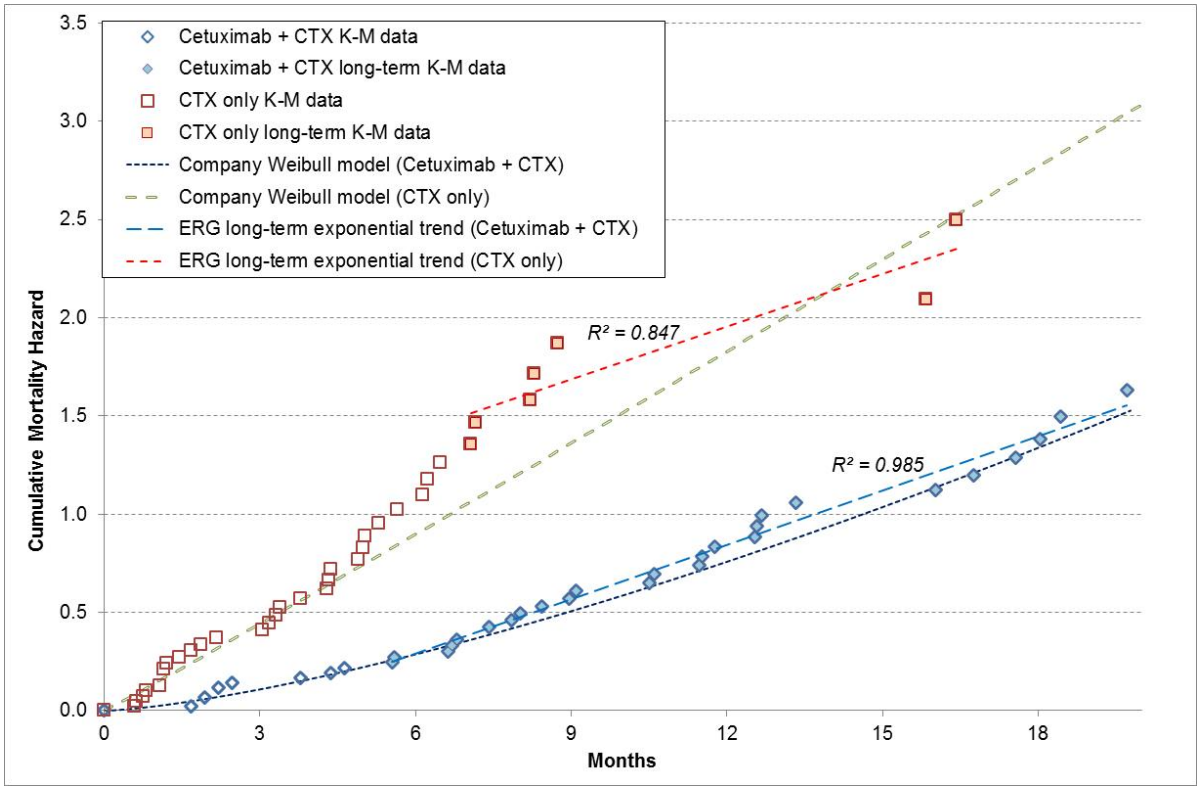

Figure 3 Comparison of Company and ERG modelling of OS cumulative hazard

CTX = chemotherapy; K-M = Kaplan-Meier analysis

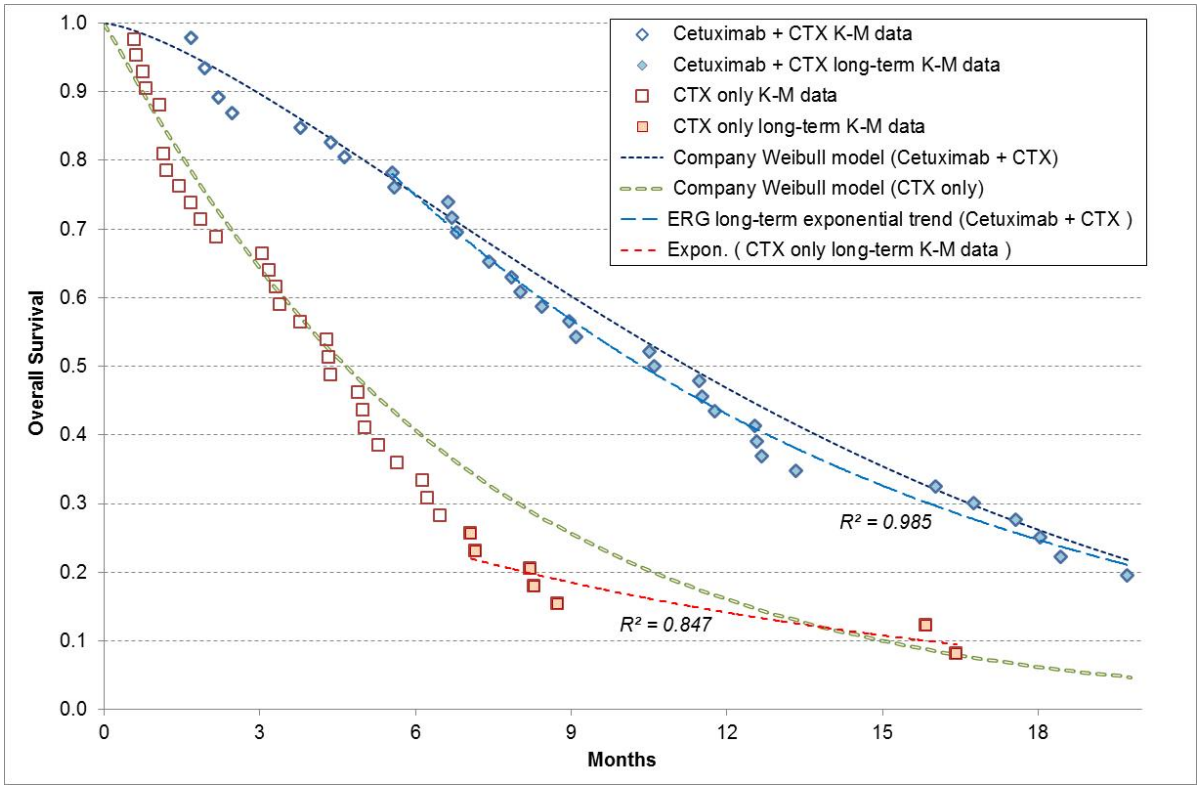

Figure 4 Comparison of Company and ERG modelling of OS

CTX = chemotherapy; K-M = Kaplan-Meier analysis

3.2.3 Post-progression survival

The ERG has not been able to estimate post-progression survival directly from trial data. However, the difference between OS and PFS estimates implies that between 40% (company model) and 36% (ERG estimate) of the OS estimate gain from treatment with cetuximab occurs after confirmed disease progression. This extent of survival gain taking place after patients' condition has deteriorated and the allocated active treatment has been terminated is unusual, and implies that some additional survival benefit can accrue in this patient group.

3.2.4 Drug acquisition costs

The ERG has re-estimated the acquisition cost to the NHS of the various products licensed for use in treating patients with head and neck carcinoma. Treatments prescribed according to a patient's BSA have been estimated for a typical UK population using the mean and standard deviation BSA for selected patients with head and neck cancer undergoing chemotherapy at three UK cancer cancers (Sacco et al.[8]). These values have been re-estimated to exclude all patients for whom the treatment intention was recorded as adjuvant, neo-adjuvant or palliative.

In addition it is necessary to apply a gender ratio when calculating a weighted average cost per cycle. The ERG has estimated costs based on three sources:

- the EXTREME clinical trial (90.3% males: 9.7% females)
- the UK audit study (73.3% males: 26.7% females)
- National Cancer Intelligence Network[9] estimate (60% males: 40% females)

Table 5 summarises the four options available to explore the sensitivity of cost-effectiveness to different assumptions. All ERG estimates of the cost of cetuximab exceed those of the company, whereas almost all other costs are lower when the ERG method is employed.

Applying the ERG estimated drug costs results in the deterministic ICER estimate increasing by £1,923 per QALY gained (trial gender balance), £1,523 (UK audit study gender balance) and £1,211 per QALY gained (NCIN[9] population estimated gender balance). The first would be preferred to ensure consistency with other trial data, and the second to match a relevant UK patient population.

Table 5 Estimated acquisition cost of 21 day cycle of treatment

Treatment	Company base case	ERG estimate using trial gender balance	ERG estimate using UK audit gender balance	ERG estimate using NCIN gender balance
Cetuximab (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab (cycles 2+)	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	£25.06	£21.35	£21.15	£21.00
5-FU	£29.49	£10.50	£10.40	£10.31
Bleomycin	£93.36	£91.11	£91.11	£91.11
Docetaxel	£24.78	£24.20	£24.20	£24.20
Methotrexate	£9.72	£6.30	£6.30	£6.30
Paclitaxel	£25.48	£21.65	£21.65	£21.65
Vinorelbine	£89.32	£95.68	£95.68	£95.68

3.2.5 Pre-progression utility values

As described above (Section 3.1.3) the ERG remains of the view that there is no strong evidence to support use of treatment-specific utility values to be used in the decision model. It is most likely that the difference in estimated values based on limited transformed trial quality of life data is largely an artefact of random variation. It is noteworthy that the calculations used to derive these estimated values are based on available data from the

whole trial population. If only EORTC survey responders from the 20% of the whole trial population with oral cavity carcinoma had been used instead, the balance of estimated pre-progression utility estimates may have been very different in either direction.

When a single common utility value is used, the estimated deterministic ICER increases by £2,883 per QALY gained.

3.2.6 Adjustment to match model predicted and trial use of cetuximab

An unusual feature of the company model is a logic 'switch' which applies a poorly explained alteration to the cost of cetuximab treatment based on a failure to reconcile the number of vials of cetuximab predicted by the company model with the number expected on the basis of recorded use during the trial. The details of the development of this feature are obscure, and it is not possible to assess whether this has been correctly estimated or not. Of particular concern is that the use of this adjustment presumes that there is a serious flaw in the company model which cannot be traced or corrected. There is no mention of the alternative possibility that accounting for trial medication issued and used may have been the source of the discrepancy. Either way, there must be serious concern that either the model or some aspects of trial data collection are unreliable.

Without any additional explanation or supporting trial evidence, it seems reasonable to assume that the attempt to reconcile vial numbers is misdirected, and that modelled cost estimates based on more traditional methods of estimating patient numbers on treatment should be relied upon. In other words the ERG considers that the 'adjustment' feature of the model should be disabled when estimating cost-effectiveness of cetuximab. This has the effect of increasing the estimated deterministic ICER by £12,002 per QALY gained.

3.2.7 Cisplatin vs carboplatin

In the original ERG report for TA172,[10] it was observed that"

> "The EXTREME trial allowed clinicians a choice between cisplatin and carboplatin for platinum-based CTX, and the base case model analysis uses the observed trial proportions (31.7% carboplatin in the intervention arm and 37.2% in the control arm). Clinical advice indicates that cisplatin is used in almost all cases in the UK."

On this basis the ERG consider it appropriate to assume that 100% patients receiving platinum therapy with receive cisplatin. This has only a minor effect by reducing the estimated deterministic ICER by £25 per QALY gained.

Details of all model amendments are provided in the Appendix.

4 RESULTS

Table 6 summarises the cost effectiveness results obtained using the revised decision model submitted by the company, together with results using the various ERG corrections and revisions described above. The ERG's preferred options result in an estimated ICER of [redacted] per QALY gained for cetuximab in combination with chemotherapy compared with standard chemotherapy for patients with recurrent or metastatic oral cavity carcinoma, an increase of more than [redacted] per QALY gain relative to the base case ICER in the company submission.

Table 6 Deterministic cost effectiveness (Cetuximab + CTX versus CTX): ERG revisions to company base case

Model scenario ERG revision	Cetuximab+CTX			CTX			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	Per QALY gained	Change
A. Company base case	[redacted]	***0.673***	***1.139***	***£10,299***	***0.319***	***0.579***	[redacted]	***0.353***	***0.560***	[redacted]	-
R1) ERG revised drug costs: a)trial gender mix b)UK audit gender mix c)NCIN gender mix	[redacted]	0.673	1.139	£10,219 £10,218 £10,217	0.319	0.579	[redacted]	0.353	0.560	[redacted]	[redacted]
R2) ERG revised PFS estimates	[redacted]	0.670	1.139	£10,478	0.317	0.579	[redacted]	0.353	0.560	[redacted]	[redacted]
R3) ERG revised OS estimates	[redacted]	0.664	1.126	£10,409	0.325	0.593	[redacted]	0.339	0.533	[redacted]	[redacted]
R4) Apply 100% cisplatin use	[redacted]	0.673	1.139	£10,244	0.319	0.579	[redacted]	0.353	0.560	[redacted]	[redacted]
R5) Common pre-progression utility value	[redacted]	0.661	1.139	£10,299	0.325	0.579	[redacted]	0.336	0.560	[redacted]	[redacted]
R6) Disable cetuximab reconciliation adjustment	[redacted]	0.673	1.139	£10,299	0.319	0.579	[redacted]	0.353	0.560	[redacted]	[redacted]
B. ERG revised base case A+R1a/b/c, R2 – R6	[redacted]	***0.650***	***1.126***	***£10,449 £10,447 £10,446***	***0.327***	***0.593***	[redacted]	***0.323***	***0.533***	[redacted]	[redacted]

5 REFERENCES

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APPENDIX: ERG AMENDMENTS MADE TO COMPANY MODEL

Most revisions are activated by a logic switch with 0 = unchanged, 1-3 = apply ERG specified modification.

Logic switches are indicated by range variables created in the 'Results' worksheet Mod_*n* where n = 1 – 4.

Summary results as used to transfer to the ERG report are shown in range 'Results'!C141:L141.

ERG Revision	Associated detail	Implementation details
R1. ERG revised drug acquisition costs with gender mix (Multi-value switch Mod_1)	Recalculation workbook "Dosing calculations final"xlsx	In Sheet 'Unit costs' A table of ERG estimated costs per cycle for each of three sources of evidence for patient gender mix has been created in the range M9:O28 Detailed derivation of each estimate is shown in workbook XXXX. **Replace** formula in cell G11 by =CHOOSE(Mod_1+1,F11*C11,M11,N11,O11) **Copy** formula in cell G11 and paste into range G12:G16 **Copy** formula in cell G11 and paste into range G23:G24 **Copy** formula in cell G11 and paste into range G26:G28
R2. ERG PFS estimates (Binary switch Mod_2)	ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival'	In Sheet 'Markov-Txarm1', **Replace** formula in cell L7 by =IF(Mod_2=1,ERGsurvival!C5,EXP(-B18 *E7^B17)) **Copy** formula in cell L7 and paste to range L8:L207 In Sheet 'Markov-Txarm2', **Replace** formula in cell L7 by =IF(Mod_2=1,ERGsurvival!E5,EXP(-B18 *E7^B17)) **Copy** formula in cell L7 and paste to range L8:L207
R3. ERG OFS estimates (Binary switch Mod_3)	ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival'	In Sheet 'Markov-Txarm1', **Replace** formula in cell K7 by =IF(Mod_3=1,ERGsurvival!D5,EXP(-B12 *E7^B11)) **Copy** formula in cell K7 and paste to range K8:K207 In Sheet 'Markov-Txarm2', **Replace** formula in cell K7 by =IF(Mod_3=1, ERGsurvival!F5, EXP(-B12 *E7^B11)) **Copy** formula in cell K7 and paste to range K8:K207
R4. Set platinum therapy to 100% cisplatin (Binary switch Mod_4)	None	In Sheet 'Resource use and Cost', **Replace** formula in cell C12 by =IF(Mod_4=1,0,69/(149+69)) **Replace** formula in cell C13 by =IF(Mod_4=1,1,149/(149+69)) **Replace** formula in cell I15 by =IF(Mod_4=1,0,80/(80+135)) **Replace** formula in cell I16 by =IF(Mod_4=1,1,135/(135+80))
R5. Pre-progression utility set to common value in both arms	None	Manually set 'Utilities!C18' drop-down menu to "Overall"
R6. Disable cetuximab usage adjustment	None	Manually set 'Resource use and cost'!C27 drop-down menu to "No"

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Merck's response to LRiG's Evidence Review Group Report

Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck (review of TA172) [ID1016]

September 2016

Executive Summary

Cancer of the oral cavity may not be recognised by the patient, particularly in the early stages when there may be limited pain or symptoms, and so it can frequently prosper. Oral cancer also has a high risk of producing second, primary tumours when they recur. For these reasons, patients with recurrent and/or metastatic oral cavity SCCHN generally present with larger more advanced stage tumours.

In patients with the oral cavity, cetuximab reduced the risk of death by 65% (HR 0.347, $p<0.0001$), resulting in an additional 6.6 months of overall survival, improving from a median OS of 4.4 months when treated with chemotherapy alone to 11.0 months when cetuximab is added to chemotherapy. Data from the EXTREME trial supports real world findings that patients in this subgroup have a worse prognosis; oral cavity patients had a median OS of 4.4 months compared to 7.4 months in the ITT when treated with chemotherapy alone. This is supported by reports that oral cavity squamous cell carcinomas may be less sensitive to chemotherapy and radiation, relative to oropharyngeal or laryngeal cancers. This is also consistent with data from Argiris et al. outlining the reduced OS in these patients compared to the patients with other H&N cancers.

This document outlines Merck's response to Liverpool's review to our resubmission of cetuximab for the treatment of head and neck cancer (squamous cell carcinoma) for CDF rapid consideration. We have addressed a number of key issues and in particular a model alteration which Liverpool have challenged despite previously stating that the approach was fully justified. Merck will continue to work with NICE to ensure access of cetuximab in a particular challenging group of patients. We ask that the committee carefully consider our justifications and if necessary provide us with the opportunity to remodel using long term five year data.

Issue 1 Adjustment in model to account for dose intensity

Description of problem	Description of proposed amendment	Justification for amendment
In Section 3.2.6. of their report, the ERG criticise the adjustment Merck made in order to match model predicted and trial use of cetuximab. Liverpool's assessment of the method – which is actually a correction for dose intensity – is flawed. More importantly it directly contradicts their appraisal of it in 2009 where they stated that it was "fully justified." In this re-appraisal, LRiG's analysis removes this adjustment. This is inappropriate, contrary to clinical evidence and does not represent how the medicine is used in real life. As such it unfairly penalises cetuximab.	The Committee should disregard Liverpool's analysis, labelled "R6) Disable cetuximab reconciliation adjustment", otherwise the underlying assumption is that there are no delayed doses or dose reductions in real life use of cetuximab and that all prescribed patients receive 100% of the dose, 100% of the time until progression. This is factually inaccurate.	Unless we accommodate dose intensity in economic models, we implicitly assume everyone will receive treatment at 100% of the prescribed dose. This is inevitably an overestimate of what happens in the real world. We are surprised that LRiG have suggested that the adjustment is not relevant. More often than not, such estimates are accommodated in economic models.[*,†,‡] Merck's model accounts for the dose intensity in the trial by applying a correction factor to cetuximab costs. The factor is derived from a comparison of the actual number of patients receiving full dose per cycle in the trial versus the projected number to receive full dose per cycle in the trial (based on posology). Merck implemented this adjustment not for the purposes of addressing any flaw or unreliability in either the economic model or the underlying trial data, but simply to ensure that the model reflects likely use of the drug in real life. Merck did not revisit the method of this adjustment in the re-

[*] Pazopanib for the first-line treatment of advanced renal cell carcinoma. https://www.nice.org.uk/guidance/ta215/documents/renal-cell-carcinoma-first-line-metastatic-pazopanib-final-appraisal-determination-guidance2

[†] Everolimus for the second-line treatment of advanced renal cell carcinoma. https://www.nice.org.uk/guidance/ta219/documents/renal-cell-carcinoma-second-line-metastatic-everolimus-final-appraisal-determination3

[‡] Ceritinib for previously treated anaplastic lymphoma kinase positive non small-cell lung cancer. https://www.nice.org.uk/guidance/ta395/resources/ceritinib-for-previously-treated-anaplastic-lymphoma-kinase-positive-nonsmallcell-lung-cancer-82602911852485

		submission because it was not a major criticism in 2009. In fact, LRiG's assessment of this adjustment at this re-appraisal directly contradicts their view of it in 2009. In the original ERG report (2009)[§], Liverpool acknowledge that 'the reduction factor' that is applied "is fully justified when carrying out a cost-effectiveness analysis". Previously the ERG preferred the use of an exponential formulation – as opposed to Merck's polynomial – to achieve this. The impact on the ICER was negligible. Merck would like to highlight that in spite of the correction, the costs of cetuximab treatment are still likely overestimated in the model. The dose intensity adjustment is made only to drug acquisition costs and not to drug administration costs (a fact noted by the ERG in 2009). Given that administration costs outweigh drug acquisition costs in the model (by [redacted]), had we accounted for the commensurate reduction in costs associated with treatment related resource use, it is likely that the ICER would be significantly improved. A number of expert UK H&N consultant oncologists provided feedback to Merck on whether dose disruptions take place when treating with cetuximab. They confirmed that in general they omit the occasional dose and in certain cases where there may be skin reactions dose interruption or discontinuation may be required. Recommendations for dose adjustments are shown in the Summary of Product

[§] Page 58, https://www.nice.org.uk/guidance/TA172/documents/head-and-neck-cancer-squamous-cell-carcinoma-cetuximab-evidence-review-group-report2

		Characteristics for cetuximab (http://www.medicines.org.uk/emc/medicine/19595). Therefore, the ERGs contention that no dose alterations take place is implausible. In summary, it would be inappropriate for NICE to consider the ERG's analysis where there is no accounting for dose intensity.

Issue 2 Pre-progression utility

Description of problem	Description of proposed amendment	Justification for amendment
LRiG claim there is no evidence that cetuximab improves quality of life (QoL) (suggesting that treatment-specific utility differences in the trial are random effects). Merck disagrees with this assessment, noting the published QoL data from the EXTREME trial published by Mesia et al. in 2010 which describes a significant beneficial effect of cetuximab on quality of life.	The base case analysis in this assessment should reflect the reality that a medicine that leads to significantly improved response rates (tumour shrinkage) versus chemotherapy alone will have some beneficial effect on quality of life. Specifically, the treatment-specific pre-progression utility estimates are more appropriate than assuming equivalence between cetuximab and chemotherapy alone.	Merck believe that the assumption that cetuximab has a positive effect on quality of life is justified by the trial evidence: 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. 3. 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'. Examples of oral cavity tumours are provided in Figure 1 below to illustrate this point. As noted above, cetuximab significantly reduces the size of these tumours and therefore can be inferred to improve the lives of patients.

Issue 3 BSA

Description of problem	Description of proposed amendment	Justification for amendment
The ERG propose that Sacco et al. is a better source of BSA values than the EXTREME trial and highlight that Merck did not adjust for gender differences in body surface area (BSA) when updating the costs in the re-submission. LRiG instead derive a BSA for head and neck cancer patients from the published UK audit study by Sacco et al., by excluding all patients for whom the treatment indication was recorded as adjuvant, neo-adjuvant or palliative in their estimate. They then apply a gender ratio to calculate the weighted average cost per cycle. Costs were estimated based on three sources of information on gender ratio: • the EXTREME clinical trial (90.3% males: 9.7% females) • the UK audit study (73.3% males: 26.7% females)	The Committee should disregard LRiG's analysis on the basis of revised BSA; it does not clearly document how BSA was re-estimated and appears to be over-estimating the mean BSA associated with the overall H&N patient population. (see Table 2, Table 3 and Table 4 in Appendices below).	The BSA should reflect recurrent/ metastatic H&N patients with tumours of the oral cavity, a severely ill sub-group of patients with bulky tumours associated with serious eating and nutritional difficulties caused by problems with swallowing. Patients with oral cavity cancer have been shown to have some of the greatest weight loss of head and neck cancer patients (Ehrsson, 2012). The mean BSA of 1.75m^2 which Merck proposes in the base case, is derived from the 'all patient' population in the EXTREME trial, 90% of whom were male. Merck contend that this BSA is more appropriate than the ERG's estimates (which we approximate to be between 1.92m^2 to 2.0m^2) and may even overestimate the BSA associated with this particularly challenging group of patients. As we described in our submission, the study by Sacco et al. (Sacco, 2010) – the ERG's source – is not specific to recurrent/metastatic patients. Furthermore, as acknowledged by the authors of this study, the H&N patient group was not large enough to allow for generalisation to the whole UK H&N population. As such, Merck contend that the data from our trial is a better representation of the BSA for R/M H&N patients and a more reliable source of data. The use of the EXTREME trial for the BSA input implies the specific gender distribution of that trial (90.3% males; 9.7% females). Merck

• National Cancer Intelligence network estimates (60% males: 40% females) Merck disagrees with this BSA adjustment. Whilst the values of the gender-specific BSA that the ERG have estimated from Sacco have not been shared with Merck, we have back-calculated the average BSA that the ERG must have used and it is clinically implausible (see Table 1 in Appendices below).		recognises that the gender ratios observed in the UK audit study or NCIN ratios better reflect the gender balance of the overall H&N patients in the UK. Reducing the proportion of males in Merck's calculation will reduce the average BSA value and in turn reduce the ICER. There is recent precedent where NICE accepted the use of a lower BSA in a metastatic colorectal cancer population compared to the UK general population with trifluridine (ID876, June 2016). Clinicians have validated this assumption by saying that you would expect metastatic patients to lose weight. If this is accepted for patients with metastatic colorectal cancer then it would be expected that the same can be accepted of a recurrent metastatic patient with a bulky tumour in the oral cavity effecting their ability to swallow and eat properly.

Issue 4 Survival modelling

Description of problem	Description of proposed amendment	Justification for amendment
LRiG claim there is a 'simpler' and more 'accurate' approach to modelling PFS and OS than Merck's use of Weibull functions. They make use of the data they received	NICE should disregard the ERG's proposal that their approach to modelling is more accurate than Merck's.	The debate about whether LRiG's preferred approach to modelling is superior to a more classic approach (fitting a range of parametric distributions and relying on goodness of fit test statistics to distinguish between them) has been inconclusively playing out in a number of

on request from Merck to re-model survival endpoints (using KM data and applying exponential extrapolations thereafter). This is a common method proposed by LiRG and in part it relies on a visual assessment of the cumulative hazard plots and a subjective assessment of whether they suggest different patterns in the underlying hazards. Merck agree that in principle this is 'simpler' but do not agree that it is more accurate.		recent NICE appraisals.[**,††,‡‡] We wish to highlight to the Committee that Merck and LRiG's analyses are based on the 2 year follow up data from the EXTREME trial whilst 5 year follow up data are now available. We highlighted this in our resubmission. However, the data were not utilised in the economic model as NICE explicitly requested that new clinical data were not to be incorporated. In light of this, the methodological discussion about which approach to extrapolation is more appropriate is a moot point. The underlying empirical data is now more mature. Given the importance of survival parameters in the economic model and the fact that a reimbursement decision for this important treatment in an underserved H&N cancer subgroup rests on this, Merck proposes that NICE re-consider their initial recommendation not to include new evidence in the model and that this process is adjusted to accommodate this.

[**] Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation‑positive malignant melanoma. https://www.nice.org.uk/guidance/ta269?unlid=87043292520167143297

[††] Dabrafenib for treating unresectable or metastatic BRAF V600 mutation‑positive melanoma. https://www.nice.org.uk/guidance/ta321.

[‡‡] Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma. https://www.nice.org.uk/guidance/ta396

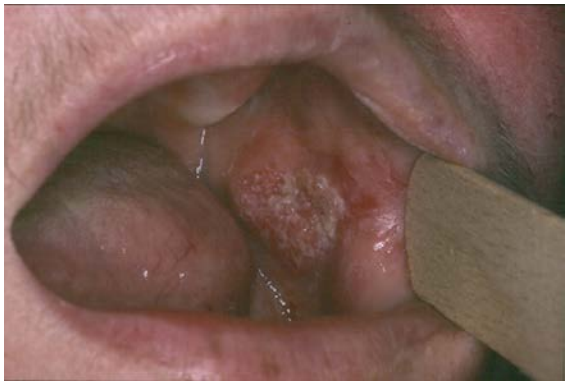
Issue 5 Cetuximab list price

Description of problem	Description of proposed amendment	Justification for amendment
On page 7 of their report, LRiG have quoted cetuximab's list price as £159.02 / 100mg vial. This is factually inaccurate.	This incorrect list price should not be utilised in NICE's documents.	The list price of cetuximab is £178.10 (BNF, Nov 2014).

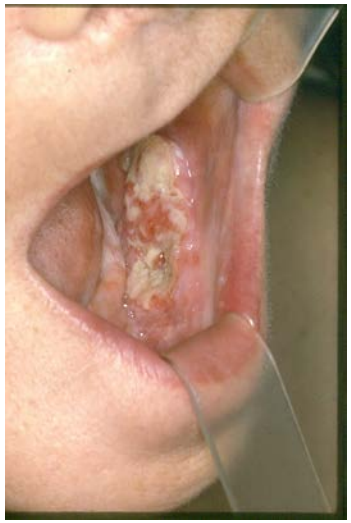
Appendices

Oral Cavity Tumours

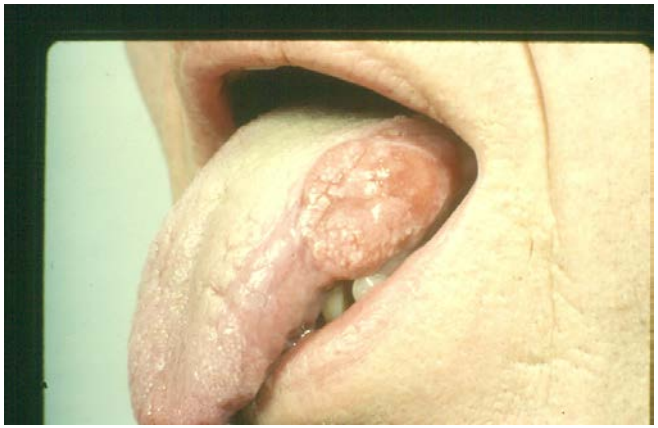
Figure 1. Oral Cavity Tumours. Kindly used by permission from Professor Kevin Harrington, The Royal Marsden.



Buccal Mucosa cancer



Buccal Mucosa cancer



Tongue cancer

MERCK'S ATTEMPTS TO REPLICATE THE ERG'S RE-COSTING

Merck can only replicate LRiG's re-costing of cetuximab and comparator treatments if we increase the BSA assumption beyond what is clinically plausible. LRiG state that they adjust the mean BSA reported by Sacco et al. by removing H&N patients receiving adjuvant, neo-adjuvant and palliative therapy, the latter of which is unreasonable as R/M H&N patients are treated palliatively with cetuximab.

This unfair and ambiguous adjustment to the BSA can be demonstrated in a number of ways.

1. *Using the mean BSA from Sacco et al. (Sacco, 2010)*

   The impact on the ICER is minimal when Merck utilises the mean BSA from Sacco et al. (males: 1.85 m^2 and female: 1.65 m^2) and applies a gender ratio derived from the same three data sources used in the LRiG's analysis to calculate a weighted average cost per-cycle.

Table 1: Deterministic cost-effectiveness using re-estimated BSA from Sacco et al. and applying three different gender ratios

BSA source	Gender ratio	Re-estimated BSA	ICER	ICER change
EXTREME trial (Merck's base case)	Trial gender mix (90.3% males 9.7% females	Merck's base case 1.75m^2	[redacted]	-
Sacco et al. (males: 1.85m2; female: 1.65m2)	Trial gender mix (90.3% males 9.7% females	1.83 m^2	[redacted]	[redacted]
	UK audit gender mix (73.3% males: 26.7% females)	1.79 m^2	[redacted]	[redacted]
	NCIN gender mix (60% males: 40% females)	1.77 m^2	[redacted]	No change

2. *Replicating the cetuximab costs derived by Liverpool ((LRiG), 2016)*

   Given that the [redacted] increase in the ICER could not be explained by the application of different gender ratios, Merck scrutinised LRiG's description of their adjustment of the Sacco et al. BSA to determine if this could better explain the increase. The vial price of cetuximab is fixed at [redacted] and the cost of treatment is dependent on a patient's BSA so Merck attempted to derive the same cetuximab costs per cycle that the LRiG proposed.

   The table below illustrates the dose, number of cetuximab vials and patient BSA required to match Liverpool's analysis. In all three scenarios where a different gender mix was used, the mean BSA would need to be above 1.9 m^2 to match the

cost per cycle in LRiG's analysis, a value which is unrealistically high for a metastatic patient with swallowing difficulties and above the mean BSA for a male H&N patient reported by Sacco et al. (Sacco, 2010) More inexplicably, the assumed BSA in the initial cycle is different to that in each subsequent cycles (a difference of 0.02 m^2).

Table 2: Mean BSA required to match the cost per cycle derived in LRiG's analysis using the EXTREME trial gender mix ((LRiG), 2016)

			Merck Base Case			EXTREME trial gender mix		
CET	**Cost per unit**	**Treatment schedule**	**BSA (m2)**	**No. of vials**	**Cost per 3-week cycle**	**BSA(m2)**	**No. of vials**	**Cost per 3-week cycle**
Initial cycle	[redacted]	400 mg/ m^2 for initial dose + 250 mg/ m^2 for subsequent weekly dose;	1.75	[redacted]	[redacted]	1.97	[redacted]	[redacted]
Cycle 2-6	[redacted]	250 mg/ m^2 weekly	1.75	[redacted]	[redacted]	2.00	[redacted]	[redacted]
Cycle 7+	[redacted]	250 mg/ m^2 weekly	1.75	[redacted]	[redacted]	2.00	[redacted]	[redacted]

Table 3: Mean BSA required to match the cost per cycle derived in LRiG's analysis using the UK survey gender mix ((LRiG), 2016)

			Merck Base Case			UK Survey gender mix		
CET	**Cost per unit**	**Treatment schedule**	**BSA (m2)**	**No. of vials**	**Cost per 3-week cycle**	**BSA(m2)**	**No. of vials**	**Cost per 3-week cycle**
Initial cycle	[redacted]	400 mg/m2 for initial dose + 250 mg/m2 for subsequent weekly dose;	1.75	[redacted]	[redacted]	1.94	[redacted]	[redacted]
Cycle 2-6	[redacted]	250 mg/m2 weekly	1.75	[redacted]	[redacted]	1.97	[redacted]	[redacted]
Cycle 7+	[redacted]	250 mg/m2 weekly	1.75	[redacted]	[redacted]	1.97	[redacted]	[redacted]

Table 4: Mean BSA required to match the cost per cycle derived in LRiG's analysis using NCIN gender mix ((LRiG), 2016)

			Merck Base Case			NCIN gender mix		
CET	**Cost per unit**	**Treatment schedule**	**BSA (m2)**	**No. of vials**	**Cost per 3-week cycle**	**BSA(m2)**	**No. of vials**	**Cost per 3-week cycle**
Initial cycle	[redacted]	400 mg/m2 for initial dose + 250 mg/m2 for subsequent weekly dose;	1.75	[redacted]	[redacted]	1.92	[redacted]	[redacted]
Cycle 2-6	[redacted]	250 mg/m2 weekly	1.75	[redacted]	[redacted]	1.95	[redacted]	[redacted]
Cycle 7+	[redacted]	250 mg/m2 weekly	1.75	[redacted]	[redacted]	1.95	[redacted]	[redacted]

More clarity is needed from LRiG on their approach to re-estimating the BSA from Sacco etc. al and how the cost of cetuximab was calculated. Furthermore, if the change in BSA has increased the cost of cetuximab treatment one would also expect the cost of chemotherapy (which is also dependent on BSA) to increase as well. In fact, the cost of chemotherapy has decreased, suggesting that Liverpool have also changed the unit cost of treatment (not documented in the ERG report (LRiG), 2016)). If any of the unit costs have been changed than Merck request an opportunity to review these alongside their sources to determine why there are discrepancies with our own inputs.

REFERENCES

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Patrelli. (2009). Clinical Cancer Advances 2009: Major Research Advances in Cancer Treatment, Prevention, and Screening—A Report From the American Society of Clinical Oncology. JCO.

Sacco. (2010). The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study. PLoS One.

Vermorken. (2008). Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. NEJM, 359;1116-27.

Issue 1 Dose Intensity adjustment

The ERG has given careful reconsideration to the question of whether dose intensity as measured in the company model can be considered reliable for adjusting the cost of cetuximab. Any dose intensity less than 100% is comprised of several distinct components including:

- Scheduled doses missed for a variety of reasons
- Scheduled doses delayed for a variety of reasons
- Scheduled doses reduced either temporarily (pending recovery from AEs)
- Scheduled doses reduced permanently
- Patients withdrawing from treatment for a variety of reasons

Some of these events have foreseeable effects on drug use and related costs, but others occur during treatment with little or no warning.

The method used in the company model uses the number of vials of cetuximab recorded as used in the EXTREME trial each cycle and compares this with the number of patients continuing to receive treatment each cycle to obtain an adjustment factor which changes over time. However, this calculation assumes a fixed number of vials per dose is used throughout the duration of the trial. By contrast in normal clinical practice some patients will vary the quantity of drug used for a combination of the circumstances described above, so that the 'normal' dose of individual patients can vary over time (rather than being 'fixed' indefinitely).

As a consequence, it can be expected that over time the 'adjustment factor' will diverge unpredictably from the simple assumption of a constant fixed dose. Without access to detailed patient-level data from EXTREME trial as well as comparable evidence from real-world experience of cetuximab use in this population it is not possible to estimate the extent to which the company adjustment method is justified or accurate.

The ERG has demonstrated the extent to which this feature of the company model is influential in determining the estimated deterministic ICER, in order to highlight the potential uncertainty involved in its use: a difference of between £0 and £12,000 per QALY gained.

Issue 2 Pre-progression utility

The cited reference (Mesia 2010) mentions both positive and negative individual effects of cetuximab+platinum based treatment compared to platinum based treatment, but comes to the following conclusion:

"The results of this analysis demonstrate that adding cetuximab to platinum–fluorouracil does not negatively affect the QoL of patients with recurrent and/or metastatic SCCHN."

Since the pre-progression utility variable relates to the overall patient experience (i.e. taking account of both positive and negative individual symptoms), the use of a common pre-progression utility value in the model is consistent with the Mesia findings.

Issue 3 BSA

There are three separate aspects of the ERG approach to costing drug doses:

- The acquisition cost of each drug used
- The source of information on the relevant demographic unit used as the basis of calculating the volume of drug required (in this case BSA)
- The method of calculating the mean cost per dose of each treatment

The acquisition cost of cetuximab used by the ERG is the company's PAS price per vial, and for all other treatments is the eMIT price at April 2016.

For estimating BSA the ERG prefer to use UK survey data published by Sacco et al. In order to consider alternative approaches to selecting the most relevant Head & Neck cancer subgroup of these data, the ERG has considered three options:

1) Using all Head & Neck cancer patients in the survey
2) Using only patients for whom the treatment intention was not adjuvant, neo-adjuvant or palliative
3) Using only patients for whom the treatment intention was not adjuvant or neo-adjuvant

Of these the ERG preferred option is (2) as this avoids recently diagnosed patients, and accords with the EXTREME clinical trial primary objective to show significant overall survival benefit.

The method of calculation used by the ERG considers the requirements of each patient individually, by estimating the proportion of patients in bands corresponding to the range of BSA values treatable with each fixed number of vials of product. This is more accurate than using the overall mean BSA value, which underestimates the wastage across the whole patient population from part-used vials. In addition, the ERG method recognises the differences in body metrics between men and women, leading to differential drug usage and costs. The balance between men and women can be derived from three sources: the patients in the EXTREME trial (overall as the M:F ratio is not available to the ERG), the UK survey patients, or the rough estimate reported by the NCIN for all Head and Neck cancer patients.

When the ERG preferred method with option (2) above is used, the estimated cost per dose of cetuximab is increased by 10.7% for the initial dose, and by 7.2% for all subsequent doses. By contrast, substitution of the EXTREME trial mean BSA value

(1.75m^2 for both men and women) for the ERG preferred BSA source reduces the average cost per dose by only 1.2% Thus, the primary driver of the increased ERG cetuximab drug acquisition cost is not the absolute BSA value adopted, but the ERG method of calculating costs at the patient level rather than as a broad overall average.

Issue 4 Survival modelling

This is not a factual error. The company prefer a different method of projective modelling to the ERG. This is a matter of opinion not of fact. The company want NICE to allow longer follow-up data to be used. This is a matter that the committee may wish to consider but is not a factual error.

Issue 5 List price

Simple typo – to correct in text