NICE National Institute for Health and Care Excellence

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

Rapid reconsideration of TA172

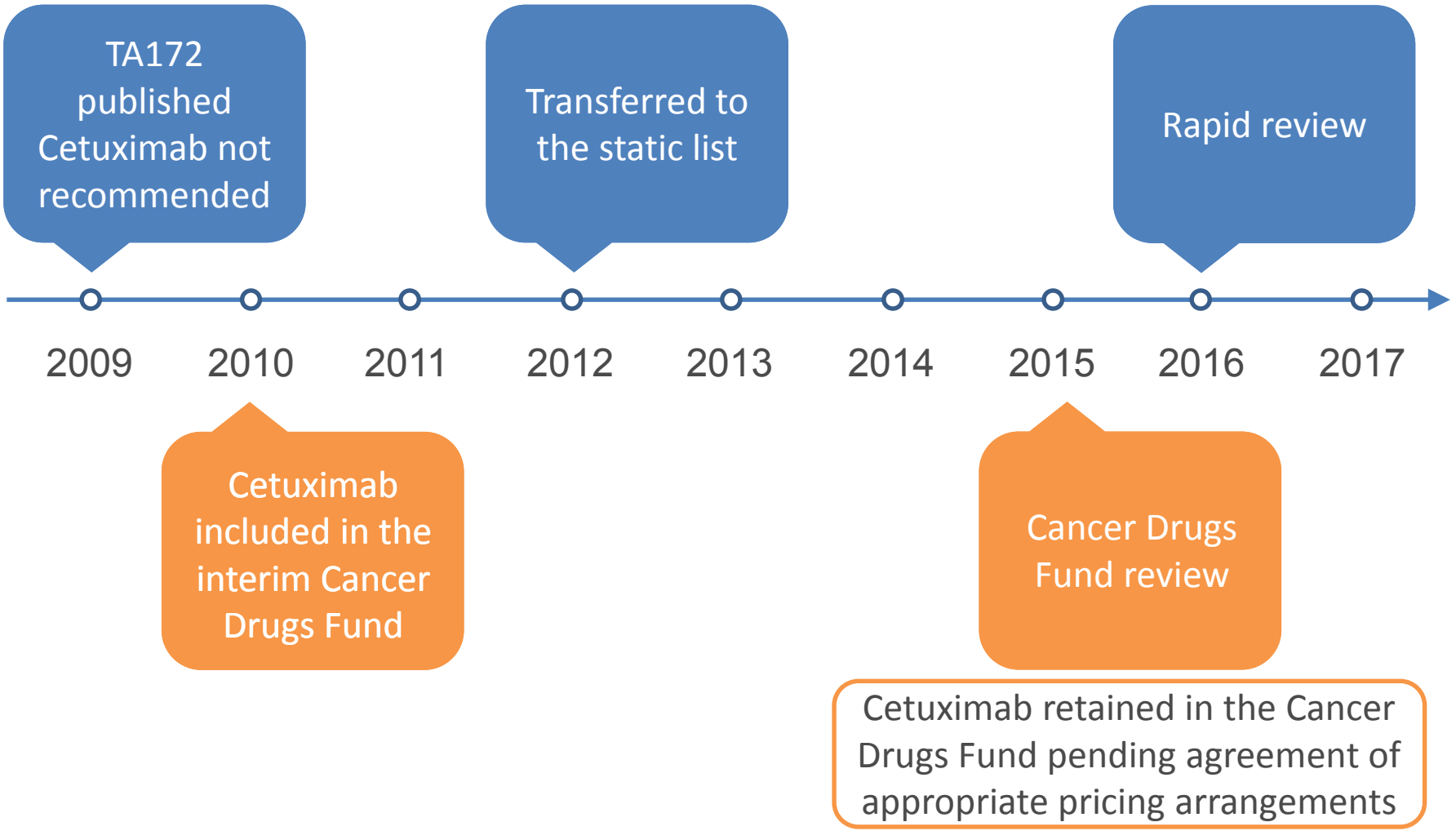
2nd appraisal committee meeting

1st February 2017

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



Evidence and committee considerations

Parameter	TA172	Accepted?	Sept 2016 meeting	Accepted?	Feb 2017 meeting
Scope	Head and neck cancer	✓	Oral cavity cancer	✗	Oral cavity cancer
Data cut	2 years	✓	2 years	✓	5 years
Base case model	Two-arm state transition model	✓	Two-arm state transition model	✓	Simple trial-based data tables
Utilities	Mismatch	✗	Mismatch	✗	Mismatch
BSA value	Trial	✗	Trial	✗	Trial
Vial usage	Model	✗	Model	✗	Trial
PAS	No	-	[redacted]%	-	[redacted]%

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Comparator and evidence

EXTREME Open-label, multicentre RCT

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

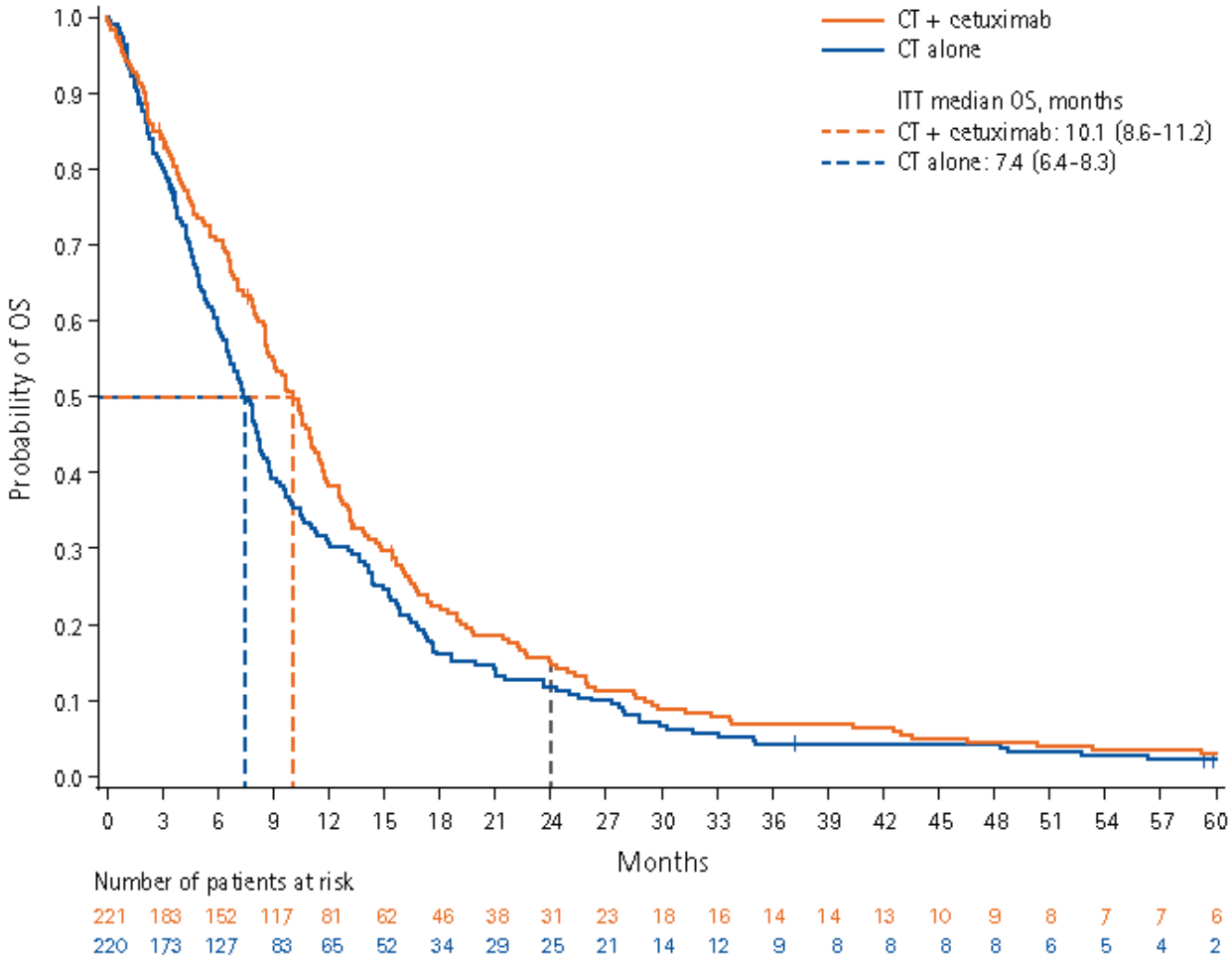
No systemic chemotherapy in the previous 6 months

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

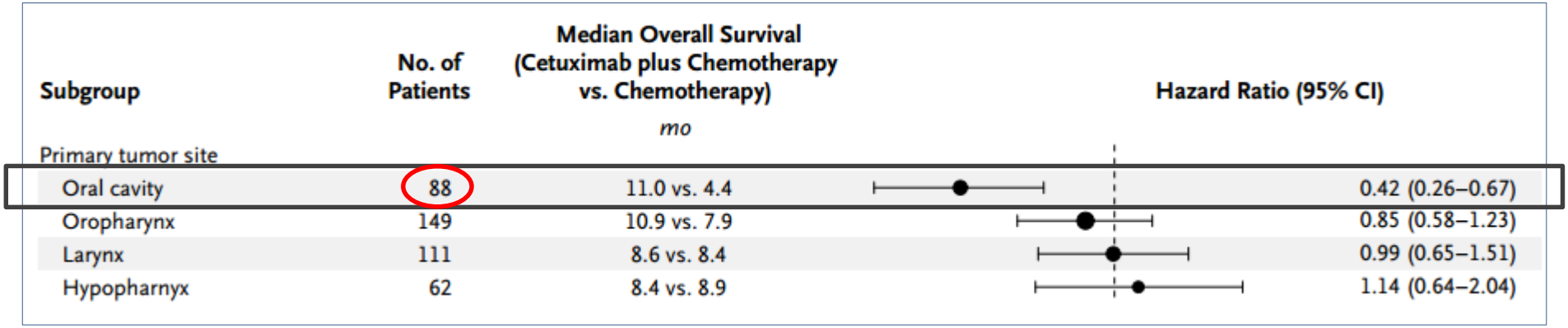
TA172 EXTREME trial
Overall survival - ITT population



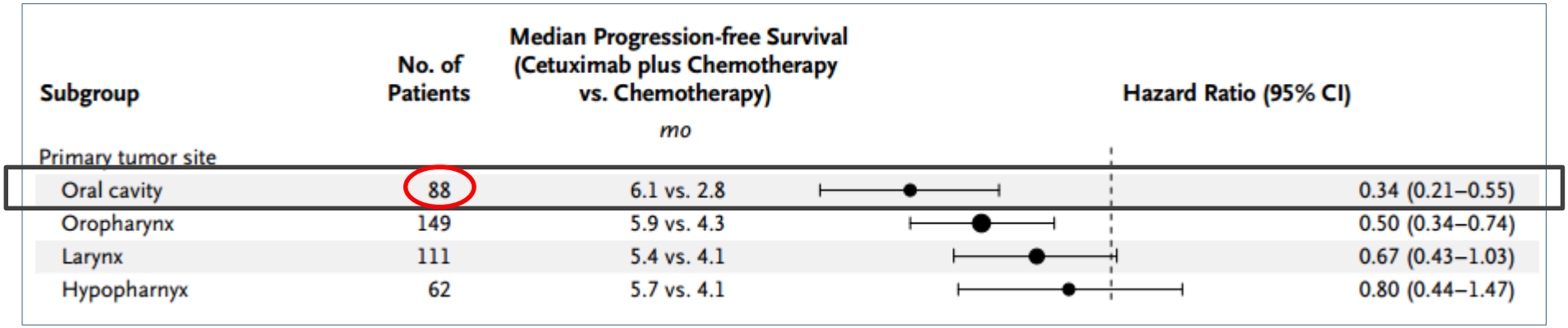
CT, chemotherapy; ITT, intention-to-treat; OS, overall survival.

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

EXTREME subgroup analysis: Primary tumour site (2-year cut-off)



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

CDF reconsideration meeting 1
Company base case:
Oral cavity subgroup (with PAS)

	Cetuximab + chemotherapy*	Chemotherapy* only	Difference
Total costs (£)	£[redacted]	£[redacted]	£[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 utilities, half cycle correction applied to costs and benefits, and 2014/15 costs

*Chemotherapy=cisplatin or carboplatin plus fluorouracil

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Source: Table 10, page 44 of the company submission

CDF reconsideration meeting 1
Company 'scenario analysis' (with PAS)

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]

*Weighted average used to amend the number of outpatient visits in line with data collected from the UK healthcare setting in 2015 ([redacted])

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

CDF reconsideration meeting 1
ERG revisions to company base case

Model scenario – Deterministic analysis	Incremental		ICER	
	Cost	QALYs	Per QALY	Change
A. Company base case	£[redacted]	0.353	£[redacted]	-
R1) ERG revised drug costs:				
a) EXTREME trial gender mix	£[redacted]	0.353	£[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]

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

ACD recommendations

Cetuximab in combination with platinum-based chemotherapy is **not recommended** within its marketing authorisation for treating recurrent or metastatic squamous cell cancer of the head and neck in adults

ACD consultation responses

No comments were received from:

- Consultees (except the company)
- Commentators
- public

Company ACD response
What's new?

- 5-year survival data from the EXTREME trial for the oral cavity cancer subgroup
- New economic model based on simple trial-based data tables
- Revised simple discount patient access scheme, increasing the level of the simple discount from [redacted]% to [redacted]% (annualised cost of cetuximab is £[redacted] with the revised PAS)
  - Agreed with the Department of Health and conditional upon positive guidance for cetuximab as a first line treatment for metastatic colorectal cancer

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Company response to ACD: Oral Subgroup

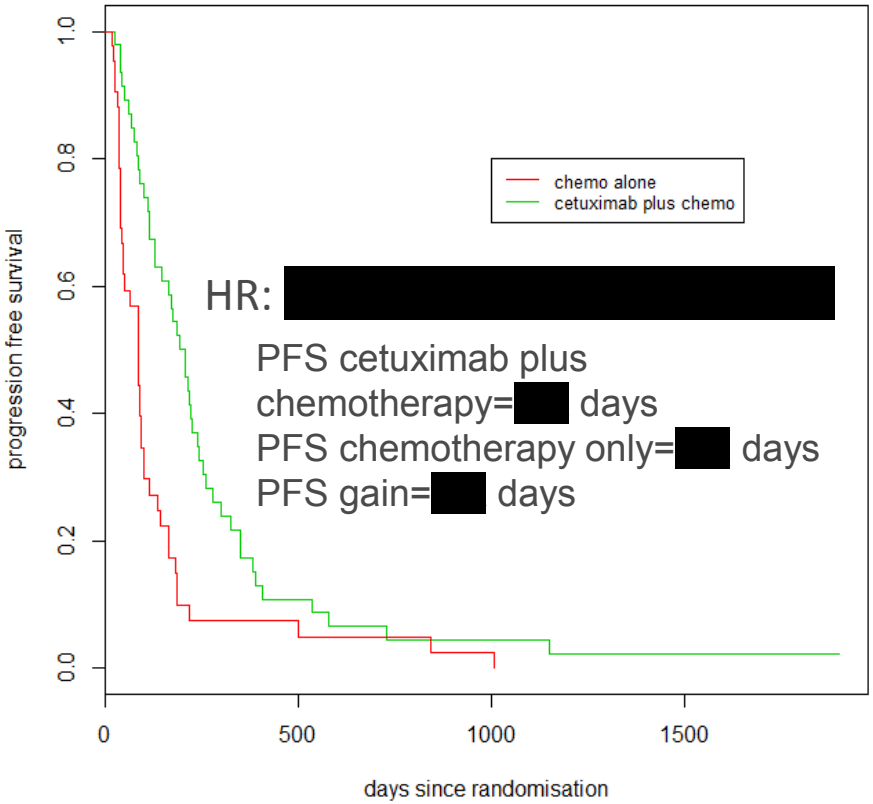
- EGFR overexpression correlates with, and predicts, poor prognosis
- Comparable results are seen with panitumumab (another EGFR inhibitor) in oral cavity patients:
  - PFS – statistically significant increase compared to ITT population (recurrent or metastatic SCCHN); OS – increase (but not statistically significant)
- Additional immunotherapeutic properties of cetuximab
  - Activates antibody-dependent cell-mediated cytotoxicity which may contribute to the pre- and post-progression states
- The 'EXTREME' regimen is considered standard of care in international guidelines produced by the NCCN and ESMO (NCCN 2016, Gregoire *et al*., 2010)
- Several ongoing phase III trials in first-line RM SCCHN include cetuximab plus platinum-based chemotherapy as the comparator

Company response to ACD: New evidence and model

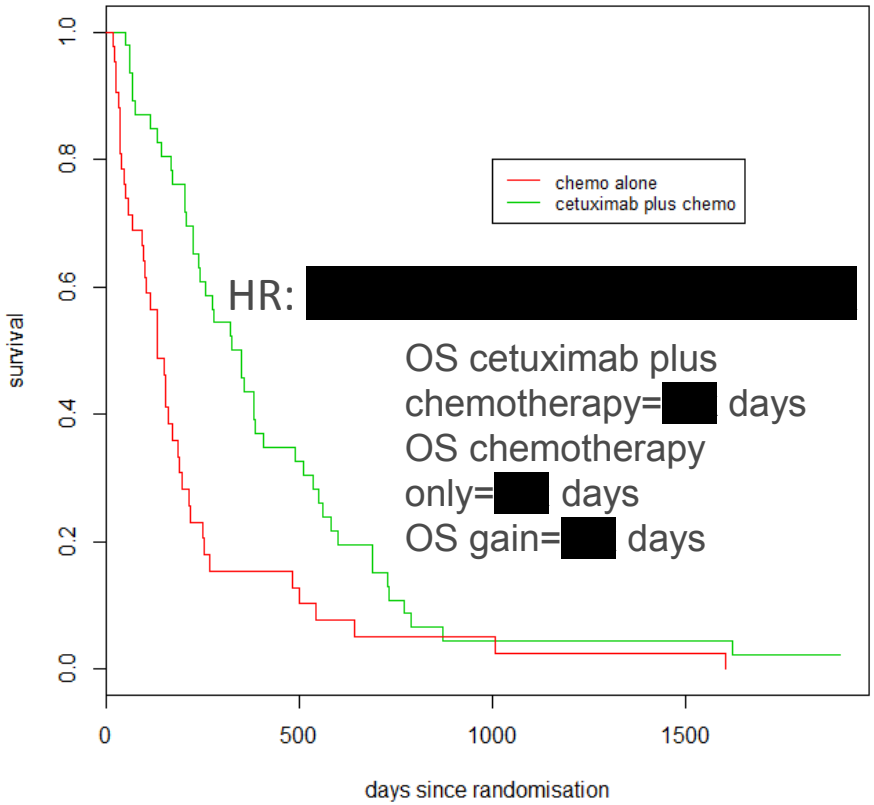
- 5-year survival data for the oral cavity cancer subgroup from EXTREME
- Trial-based model in the base case to eliminate uncertainties associated with extrapolation
  - Costs of treatment estimated from the average total number of whole vials delivered to (trial based) patients and the unit cost of a vial - avoids the need to retrospectively apply a 'dose-intensity' correction
  - Treatment-related costs estimated from the average number of dosage sessions per treatment per patient and the cost per session
  - Five year horizon without discounting
- Revised simple discount patient access scheme
  - Conditional upon positive guidance for cetuximab as a first-line treatment of metastatic colorectal cancer

5-year data: Oral cavity subgroup

Progression-free survival



Overall survival



Previous analysis (2 year cut-off): median PFS (months) HR 0.34 (0.21 to 0.55)
median OS (months) HR 0.42 (0.26 to 0.67)

Company's new base case

	Cetuximab + chemotherapy*	Chemotherapy* only	Difference
Total costs (£)	£[redacted]	£9,267	£[redacted]
QALYs gained	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			£[redacted]

Using a weighted average to amend the number of outpatient visits in line with data collected from the UK healthcare setting in 2015 ([redacted]), the company suggests that the administration costs are overestimated by [redacted]% for UK practice (£[redacted] versus £[redacted]). This results in an ICER of £[redacted]/ QALY gained

*Chemotherapy=cisplatin or carboplatin plus fluorouracil

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Source: Figure 20, page 22 of the company response to the ACD

Company scenario analyses: Extrapolation-based model (with PAS)

- Same 3-state partitioned survival model as the trial-based model (executable model was not provided by the company)
  - Survival extrapolated using (arbitrary) Weibull curves
  - Same inputs as the trial-based model with additional annual discounting (3.5% costs and benefits) and full probabilistic sensitivity analysis
  - Five-year time horizon
- The deterministic ICER for 100% weekly dosing is £[redacted]/QALY and the probabilistic ICER is £[redacted]/QALY. When a weighted average of the market research dosing assumptions ([redacted]) are used, the ICER is £[redacted]/QALY

Source: Page 25 of the company response to the ACD

ERG critique of ACD response

- Focussed on the new base case analysis
  - New 5-year OS and PFS evidence (available only in graphical form)
  - Assessed the accuracy/validity of the other data and parameter values used to generate the new base case economic results
- The revised electronic decision model supplied by the company is incompatible with the new non-model base case
  - Uses a different basis for representing overall survival and progression-free survival. Cited by the company to indicate the probabilistic cost-effectiveness results that might be expected with the new data
  - This has not been critiqued by the ERG

ERG critique of company base case: Progression-free survival

- All oral cavity patients in the chemotherapy only arm have suffered an event except for 1 patient censored early in the trial, however
- 1 patient in the cetuximab plus chemotherapy arm remained event-free after five years follow-up
- This patient alone contributed additional estimated PFS benefit to the analysis for more than [redacted]
- The ERG consider that this could introduce substantial random error in favour of the cetuximab plus chemotherapy arm on the basis of the timing of a single patient event

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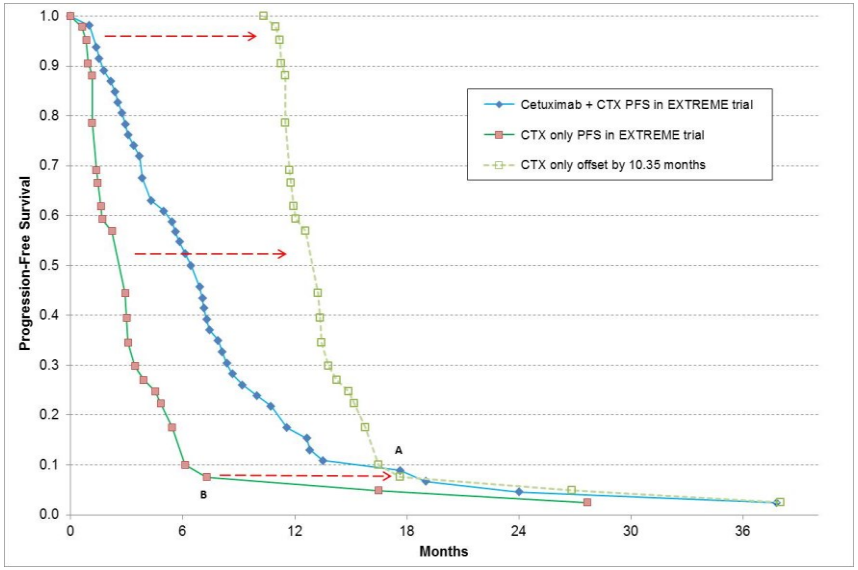
ERG critique base case: Progression-free survival

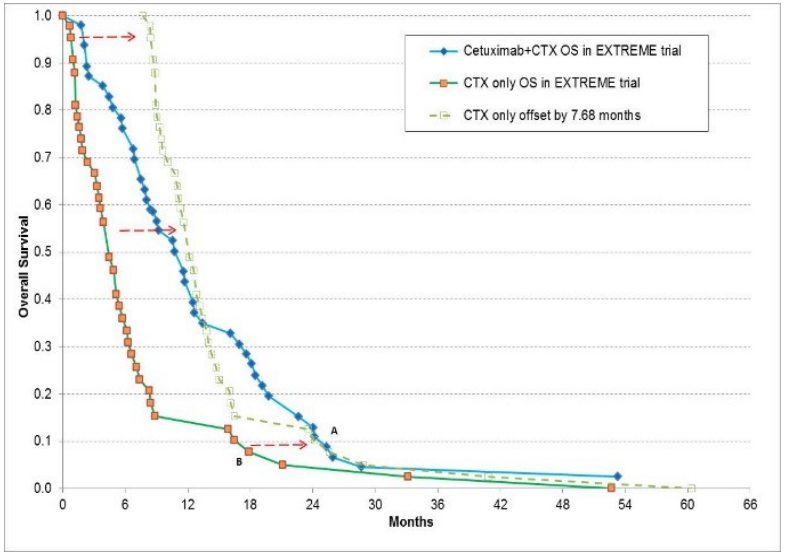


The Kaplan-Meier curves from both arms plateau when 10% of patients are estimated to be event-free

- The ERG estimated the PFS advantage for cetuximab plus chemotherapy versus chemotherapy only by comparing the area under the Kaplan-Meier curves up to the inflection point after which the curves overlay each other
- The estimated mean PFS gain is [redacted] days ([redacted] days for cetuximab plus chemotherapy less [redacted] days for chemotherapy only), [redacted] days less than the mean PFS gain estimated by the company

Source: Figure 1, page 5 of ERG critique of the company ACD response

ERG critique: Overall survival



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

- The overall survival curves in the five-year follow-up data also show equivalence of the long-term data
- The ERG estimates a mean gain in OS attributable to cetuximab of [redacted] days ([redacted] days for patients treated with cetuximab plus chemotherapy compared with [redacted] days for patients treated with chemotherapy only), [redacted]% less than the company estimated mean difference of [redacted] days ([redacted] days for cetuximab plus chemotherapy and [redacted] days for chemotherapy only)

Source: Figure 3, page 7 of ERG critique of the company ACD response

ERG critique: Post-progression survival

- Mean post-progression survival gain attributable to cetuximab (estimated as the difference between overall survival and progression-free survival) indicates that **more than a third** of the overall survival benefit may arise during the post-progression period
- This is uncommon in trials for advanced cancer, where the disease often reverts to the typical progressive disease trajectory, independent of the choice of prior treatment

ERG critique: Treatment costs (1)

- The company has used the average number of 100 mg vials of cetuximab per person from the EXTREME trial and the number of treatment sessions to estimate the average dose of cetuximab per patient session to be 253 mg (3 vials, *including the initial session which requires a higher dose*)
- The dosing regimen for cetuximab is 400 mg/m^2 for the initial dose, followed by 250 mg/m^2 weekly thereafter. However the company model incorrectly assumes that the 'cumulative dose received' is in mg rather than mg/m^2
- BSA data for the oral cavity subgroup of the EXTREME trial have not been provided by the company. Using BSA values from a UK survey of head and neck cancer patients (Sacco *et al*., 2010), the gender balance in the EXTREME trial, and adjusting for wastage due to partly used vials, the ERG calculate the mean prescribed dose of cetuximab per patient session to be 8 vials for the initial treatment and 5 vials for subsequent weekly treatments
- The company model does not include an allowance for wastage due to missed doses

ERG critique: Treatment costs (2)

- The company states that in a survey of UK patients receiving cetuximab, [redacted]. However it is not clear how this was managed in terms of the total dose administered per cycle, the extent of sub-optimal dosing or the impact of these different regimens on treatment outcomes
- The ERG considers that it is not appropriate to model the patient survival outcomes reported in the EXTREME trial whilst also reducing treatment
- Since EXTREME is the only source of evidence relevant to the small subgroup being considered, the ERG believes that there is too much uncertainty attached to this deviation from the trial evidence to warrant the proposed amendment to the cost-effectiveness analysis

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ERG critique: Health state patient utility

- The company use different pre-progression utilities for cetuximab and chemotherapy only patients (but pooled utilities for post-progression)
- However there is no statistical justification for not also using a common pooled estimate for the pre-progression health state
- The ERG considers the data available from the EXTREME trial is insufficient to infer reliable differential utility effects between competing treatments
  - There are only 52 observations in total (33 from an unknown number of cetuximab patients and 11 from an unknown number of chemotherapy patients)
  - Knowing whether a patient is randomized to receive the interventional treatment, as in this trial, can influence patient responses to quality of life questions
  - Patients with a good response to treatment are more likely to participate in completing repeated quality of life questionnaires
- The ERG considers that a pooled PFS utility value of 0.683 should be applied to both treatment arms

ERG critique: Discounting

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

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ERG critique: End of life criteria

	Oral cavity subgroup
Life expectancy normally <24 months	7.4 months (mean)
Extension to life normally >3 months	6.4 months (mean)

- Cetuximab plus chemotherapy fits the ‘end of life’ criteria

ERG revisions to the new company base case

Model Scenario	Incremental costs	Incremental QALYs	Estimated ICER (£/QALY)	ICER change
Company revised base case	£[redacted]	[redacted]	£[redacted]	-
ERG survival analysis (PFS/PPS/OS)	£[redacted]	[redacted]	£[redacted]	£[redacted]
ERG drug costing	£[redacted]	[redacted]	£[redacted]	£[redacted]
Common PFS utility value	£[redacted]	[redacted]	£[redacted]	£[redacted]
Applying discounting	£[redacted]	[redacted]	£[redacted]	£[redacted]
ERG revised base case	£[redacted]	[redacted]	£[redacted]	£[redacted]

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Source: Table 2, page 11 of ERG critique of the company ACD response

Issues for discussion

- Does the committee consider that there is sufficient evidence to support the estimate of effectiveness based on the oral cavity cancer subgroup data?
- Does the 5-year follow-up data support the estimate of overall survival gain for the oral cavity subgroup?
- Are the company calculations or the ERG modifications more appropriate?
- Are the end-of-life criteria met in the oral cavity subgroup?
- What is the most plausible ICER?

Effect of ERG changes on the ICER

ERG changes			Revised ICER		
Cetuximab cost	PFS pooled utility	PFS/OS estimates	Undiscounted	Discounted	
No	**No**	**No**	£[redacted]	£[redacted]	Company revised base case
No	No	Yes	£[redacted]	£[redacted]	
No	Yes	No	£[redacted]	£[redacted]	
No	Yes	Yes	£[redacted]	£[redacted]	
Yes	No	No	£[redacted]	£[redacted]	
Yes	No	Yes	£[redacted]	£[redacted]	
Yes	Yes	No	£[redacted]	£[redacted]	
Yes	**Yes**	**Yes**	£[redacted]	£[redacted]	ERG preferred scenario