

7.03 CETUXIMAB, Solution for I.V. infusion 100 mg in 20 mL Solution for I.V. infusion 500 mg in 100 mL, Erbix[®], Merck Serono Australia.

1 Purpose of Application

- 1.1 The resubmission requested for a Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) listing for cetuximab, in combination with platinum-based chemotherapy (CT), for the treatment of patients with previously untreated recurrent and/or metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN). The last consideration by the PBAC of cetuximab for this indication was in March 2016; however that submission had focused on a subgroup of RM SCCHN patients with oral cavity cancers.
- 1.2 The basis for listing was a cost effectiveness comparison to platinum CT only.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (RM SCCHN)
Intervention	Cetuximab plus platinum chemotherapy (cisplatin or carboplatin) plus 5-fluorouracil (5-FU)
Comparator	Platinum based chemotherapy (CT) (cisplatin or carboplatin) plus 5-fluorouracil (5-FU)
Outcomes	Overall survival (OS) is the primary outcome, progression free survival (PFS), response rate, quality of life, safety
Clinical claim	Cetuximab plus platinum CT and 5-FU followed by maintenance with cetuximab monotherapy is more effective than platinum CT and 5-FU only at improving OS, PFS and overall response rate with a manageable increase in adverse events.

Source: Table 1.1.1, p13 of the resubmission

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price Max Amt	Proprietary Name and Manufacturer
CETUXIMAB Injection, 100 mg/20 mL Injection, 500 mg/100 mL	880 mg	0	published prices: Public: \$2,999.38 Private: \$3,078.86 effective prices ^a Public: \$ Private: \$	Erbix Merck Serono Aust

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Category/Program:	Section 100 (Efficient Funding of Chemotherapy (EFC – Private Hospital) Section 100 (Efficient Funding of Chemotherapy (EFC – Public hospital))
PBS indication:	Recurrent and/or metastatic squamous cell carcinoma of the head and neck
Treatment phase:	Initial treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be recurrent or metastatic SCCHN AND The condition must be previously untreated AND The treatment must be commenced in combination with platinum-based chemotherapy

^a The resubmission nominated a [REDACTED] % rebate from the published price, and also a cap of [REDACTED] reimbursed infusions per patient.

Name, Restriction, Manner of administration and form	Max Amt	No. of Rpts	Dispensed Price Max Amt	Proprietary Name and Manufacturer
CETUXIMAB Injection, 100 mg/20 mL Injection, 500 mg/100 mL	550 mg	22	published price Public: \$2,027.53 Private: \$2,093.39 effective prices ^a Public: \$ [REDACTED] Private: \$ [REDACTED]	Erbitux Merck Serono Aust

Category/Program:	Section 100 (Efficient Funding of Chemotherapy (EFC – Private Hospital) Section 100 (Efficient Funding of Chemotherapy (EFC – Public hospital))
PBS indication:	Recurrent and/or metastatic squamous cell carcinoma of the head and neck
Treatment phase:	Continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have progressive disease

^a The resubmission nominates a [REDACTED] % rebate from the published price, and also a cap of [REDACTED] reimbursed infusions per patient.

2.1 The resubmission proposed a [REDACTED] % rebate on the nominated published prices. This was increased from the proposed rebate of [REDACTED] % in its March 2016 submission. In the Pre-PBAC response the sponsor proposed a revised net effective price of \$ [REDACTED] per 100 mg vial, which is a further [REDACTED] % reduction from the proposed price in the March 2018 resubmission. The resubmission also proposed a subsidisation cap of [REDACTED] infusions for each patient. Details on how the cap will be implemented were not provided by the resubmission. The comparison between the risk sharing agreements in the previous submission with the current resubmission is summarised in Table 2.

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Table 2: Comparison of ex-manufacturer price per vial with previous submission

Vial size	March 2016 submission			March 2018 resubmission		
	Published Price/Vial	Rebate	Effective Price/Vial	Published Price/Vial	Rebate	Effective Price/Vial
100mg	\$341.00	%	\$	\$323.95	%	\$*
500mg	\$1,705.00	%	\$	\$1,619.75	%	\$*
Dose cap						

Source: constructed during evaluation

* Price proposed in the pre-PBAC response \$/100 mg vial, the equivalent price for the 500 mg vial would be \$ (5 x \$).

- 2.2 The key differences between the proposed restriction and that requested in the March 2016 submission were: i) the expansion of the listing to include all patients with RM SCCHN rather than limiting use to a subset of patients with oral cavity cancers only and ii) the removal of the clinical criteria for patients to have World Health Organisation (WHO)/Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
- 2.3 The lack of definition of a patient performance status meant the requested restriction was broader than the trial population. The main evidence supporting the resubmission (the EXTREME trial) had enrolled patients with Karnofsky performance score (KPS) ≥ 70 , which corresponds to either ECOG PS of 0-1¹ or 0-2² depending on publication. There is a paucity of data for the efficacy of cetuximab in patients with KPS <70 or ECOG PS >2. The PBAC noted that the EXTREME trial enrolled patients with the equivalent of a performance status 0-2 and considered that inclusion of the clinical criteria for patients to have ECOG PS of 0-2 would be appropriate.
- 2.4 The requested condition “squamous cell carcinoma of the head and neck” (SCCHN) is not a defined term in the SNOWMED Clinical Terminology Australian Release. Although some specific sites such as squamous cell carcinoma of the larynx/oropharynx/mouth/ buccal mucosa/lip/tongue are defined terms, these terms may not fully incorporate the intended treatment population. Existing cetuximab listings are for “metastatic colorectal cancer” and “Stage III, IVa or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx”. The PBAC considered that the requested indication in this resubmission should be modified to read; recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx. This is consistent with the trial population and with other requests for listing in these conditions.

¹ Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

² Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer. 1996 Jun;32A(7):1135-41.

- 2.5 The PBAC considered that the clinical criterion “that the condition must be previously untreated” should remain in the restriction.

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Background

- 3.1 Cetuximab was approved by the TGA for the treatment of patients with SCCHN in combination with platinum-based chemotherapy for recurrent or metastatic disease on 5 January 2010. Cetuximab is also TGA-approved for treatment of patients with Epithelial Growth Factor Receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer (in combination with other agents or monotherapy) and for the treatment of patients with SCCHN in combination with radiotherapy.
- 3.2 Cetuximab, in combination with radiotherapy, is currently PBS-listed for the treatment of patients with Stage III, IVa or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx, who are unable to tolerate or have a contraindication to cisplatin. Cetuximab is also PBS listed for the treatment of metastatic colorectal cancer.

Previous PBAC consideration

- 3.3 Table 3 summarises the outstanding matters of concern noted by the ESC and the PBAC with respect to the March 2016 submission for cetuximab for RM SCCHN and how they were addressed in the resubmission.

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Table 3: Summary of outstanding matters of concern

Component	Matter of concern	How the resubmission addresses it
Requested restriction population	The PBAC considered that the sponsor's request to limit cetuximab use to the subgroup of patients with RM SCCHN of the oral cavity was not supported and that ITT analysis of the trial was more informative for determining the clinical benefit of cetuximab. (cetuximab March 2016 PSD 7.4). The PBAC also considered there to be a high risk of leakage from the oral cavity only population (cetuximab March 2016 PSD 7.2).	The population in the requested restriction changed from oral cavity only subpopulation to all patients with RM SCCHN.
Previous treatment	The ESC noted that eligible patients may have received prior cetuximab. The effect of prior cetuximab use was unknown. The requested PBS-listing limited use of cetuximab in previously untreated patients, but the TGA-approved indication did not limit use to this population (cetuximab March 2016 PSD 3.2).	The sponsor previously proposed to remove the clinical criterion of "previously untreated" to provide consistency with the TGA-approved indication (cetuximab March 2016 PSD 2.1). However this clinical criterion remained in the resubmission.
Magnitude of benefit	The PBAC considered that the claim of superior comparative effectiveness was reasonable for the overall ITT population with respect to overall survival, progression-free survival and response rates, although the magnitude of the benefit (such as a median survival of 2.7 months) was small (cetuximab March 2016 PSD 7.5).	Unchanged. The resubmission did not provide new clinical evidence for cetuximab.
Safety claim	The previous submission made no comparative safety claims. The PBAC considered cetuximab + CT to be inferior in safety to CT only treatment (cetuximab March 2016 PSD 7.6).	The resubmission claimed that cetuximab + CT is inferior in safety compared to CT only with a manageable side effect profile.
Anti-EGFR antibody Class effect	The PBAC considered it would be helpful if additional evidence corroborating the benefit of anti-EGFR antibodies in the setting of RM SCCHN could be identified (cetuximab March 2016 PSD 7.7).	A literature search and meta-analysis of anti-EGFR antibodies in first line RM SCCHN was presented. Only trials for panitumumab were identified in addition to EXTREME for cetuximab.
Model uncertainties	In addition to uncertain clinical input which affected the economic uncertainty, the PBAC also noted a number of other uncertainties in the model which favoured cetuximab including the choice of extrapolation method, the subgroup extrapolation in the context of limited data, the source of the utility values, an optimistic time horizon and drug administration costs. (cetuximab March 2016 PSD 7.8)	Extrapolation and time horizon remained unchanged in the resubmission (see economic analysis). However, the utility source was changed to Greenhalgh et al 2008. Drug administration costs were further reduced and were biased in favour of cetuximab.

Abbreviations RM = recurrent or metastatic, SCCHN = squamous cell carcinoma of the head and neck, ITT = intention to treat, PSD = public summary document, CT = chemotherapy, EGFR = epithelial growth factor receptor, Source: Cetuximab March 2016 PSD

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 SCCHN was defined by the resubmission as cancers of the head and neck which originate from squamous cells found in mucosal lining of the upper aero digestive tract. Sites for SCCHN include the oral cavity, nasal cavity, paranasal sinuses, pharynx and larynx. Approximately 50-60% of SCCHN patients present with locally advanced or metastatic disease. Median overall survival for patients with RM SCCHN treated with CT only had been reported at 6-9 months.

- 4.2 The resubmission proposed that cetuximab will be administered alongside platinum based CT in patients in whom systemic therapy for RM SCCHN is appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The nominated comparator was platinum CT only. The PBAC previously accepted this as the appropriate comparator for RM SCCHN in the oral cavity subgroup and agreed with ESC that this is also the appropriate comparator for the broader RM SCCHN population.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician outlined the impact of the disease on patients' ability to talk, eat, and breath, giving context to the acceptability of a high level of AEs from treatment to prevent death from local disease. The clinician also discussed the natural history of the disease, noting that SCCHN caused by viral infection tends to have a better prognosis than that caused by tobacco use and alcohol consumption, and that cetuximab is effective in SCCHN from either cause. The clinician also discussed how cetuximab would be used in practice and addressed other matters in response to the Committee's questions. The clinician noted that over-recruitment in clinical trials suggests that the current standard of care is not considered best practice. The PBAC considered that the hearing was informative as it provided a clinical perspective and quality of life factors considered when treating patients with RM SCCHN.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (9) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with cetuximab including the reduction in hospital admissions and medications, and fewer side effects affecting the patient's speech, ability to swallow and eat. The comments noted that many of these patients are younger, otherwise healthy individuals and that there is a need for additional, well-tolerated treatments in this patient population as current treatment options are limited.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the cetuximab submission on the basis of an overall survival (OS) and progression free survival (PFS) benefit. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for cetuximab, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent

the grades with substantial improvement)³, based on a comparison with chemotherapy alone.

Clinical trials

- 6.4 The resubmission was based on one head-to-head trial comparing cetuximab + CT to CT only (n=442) (EXTREME). The same evidence was presented in the March 2016 submission. The ESC noted that following previous PBAC advice (cetuximab March 2016 PSD, 7.4), the submission sought listing for the whole trial population rather than the oral cavity subgroup in the trial. The PBAC agreed with ESC that this was appropriate.
- 6.5 Following previous PBAC advice (cetuximab 2016 PSD, 7.7), an additional meta-analysis of anti-EGFR antibodies (cetuximab and panitumumab) in RM SCCHN was also presented (see Section 2.6). Only trials for panitumumab were identified by the resubmission in addition to cetuximab in first line treatment of RM SCCHN.
- 6.6 Details of the trials presented in the resubmission are provided in the table below.

³ Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 26:1547-73, 2015

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Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
EXTREME	Cetuximab (Erbix®) in combination with cisplatin or carboplatin and 5-fluorouracil in the first-line treatment of subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck ("EXTREME") (EMR 62 202-002)	8 February 2008
	Vermorken JB et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer.	New England Journal of Medicine 2008; 359 (11): 1116-27
	Mésia R et al. Quality of Life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck.	Annals of Oncology 2010; 21 (10): 1967-73
	Licitra L et al. Evaluation of EGFR copy number as a predictive biomarker for the efficacy of cetuximab in combination with chemotherapy in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck: EXTREME study.	Annals of Oncology 2011; 22: 1078-87
	Licitra L et al. Predictive value of epidermal growth factor receptor expression for first-line chemotherapy plus cetuximab in patients with head and neck and colorectal cancer: Analysis of data from the EXTREME and CRYSTAL studies.	European Journal of Cancer 2013; 49(6): 1161-8
Vermorken JB et al. Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial.	Annals of Oncology 2014; 25: 801–7	
Other EGFR in RM SCCHN trials		
SPECTRUM	Vermorken JB(1), Stöhlmacher-Williams J, Davidenko I, Licitra L, Winquist E, Villanueva C, Foa P, Rottey S, Skladowski K, Tahara M, Pai VR, Faivre S, Blajman CR, Forastiere AA, Stein BN, Oliner KS, Pan Z, Bach BA; SPECTRUM investigators. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial.	Lancet Oncol. 2013 Jul;14(8):697-710.
PARTNER	Wirth L.J., Dakhil S., Kornek G., Axelrod R., Adkins D., Pant S., O'Brien P., Debruyne P.R., Oliner K.S., Dong J., Murugappan S. PARTNER: An open-label, randomized, phase 2 study of docetaxel/cisplatin chemotherapy with or without panitumumab as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck	Oral Oncology 2016 61 (31-40).

Source: Table 2.2-2, pp38-39 of the resubmission and Appendix 3 of the resubmission

6.7 The key features of the direct randomised trials are summarised in the table below.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Cetuximab + CT (cisplatin or carboplatin + 5-FU) vs CT only (cisplatin or carboplatin + 5-FU)						
EXTREME	442	R, OL 19 months ^a	Low	First line RM SCCHN	OS, PFS, response	OS, PFS and response used in different steps
Panitumumab + CT (cisplatin or carboplatin^b + 5-FU) vs CT only (cisplatin or carboplatin^b + 5-FU)						
SPECTRUM	657	R, OL 18 months ^c	Low	First line RM SCCHN	OS, PFS, response	Not used
Panitumumab + CT (cisplatin or carboplatin^d + docetaxel) vs CT only (cisplatin or carboplatin^d + docetaxel)						
PARTNER	113	R, OL 50 months ^e	High ^f	First line RM SCCHN	PFS, OS, response	Not used

Abbreviations: CT = Chemotherapy; 5-FU = 5-fluorouracil; RM = recurrent or metastatic; SCCHN = squamous cell carcinoma of the head and neck; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.

^a Median follow up for cetuximab + CT arm 19.2 months and CT only arm 18.2 months. Maximum follow up for patient alive was 26 months

^b All patients started on cisplatin and may switch to carboplatin if creatinine clearance <50mL/min or had >grade 2 neurotoxic adverse event

^c Planned 18 months follow up per patient. Median follow up in panitumumab + CT 44 weeks and CT only 35 weeks.

^d All patients started on cisplatin and may switch to carboplatin if creatinine clearance <60mL/min or had >grade 2 neurotoxic adverse event. Patients in CT only arm could switch to panitumumab after progression of disease

^e Duration not specified in trial publication but Kaplan Meier curves showed data up to 50 months.

^f High due to cross over from CT only to panitumumab + CT and open label trial design introduce bias for subjective outcomes

Source: constructed during evaluation using information from Vermorken 2008, Vermorken 2013 and Wirth 2016

6.8 The EXTREME trial was an open label trial that compared treatment with cetuximab + CT versus CT only in first line treatment of RM SCCHN. The chemotherapy regimen administered in the trial consisted of carboplatin or cisplatin in combination with 5 – fluorouracil (5-FU). The overall median trial follow-up was 19.2 and 18.2 months for cetuximab + CT and CT only arms of the trial, respectively. Although the risk of bias was low for the primary outcome of OS which was an objective outcome, the open-label design of the trial meant that more subjective outcomes such as PFS, response rate, quality of life (QoL) and self-reported adverse events may be biased.

6.9 SPECTRUM and PARTNER were two open label trials of panitumumab (an alternate anti-EGFR antibody) in first line RM SCCHN. Both trials compared panitumumab + CT versus CT only; however PARTNER also permitted use of docetaxel in both treatment arms. Further, the PARTNER trial had allowed patients treated with CT only to cross over and receive panitumumab after progression, whereas in the EXTREME and SPECTRUM trials, crossover was not permitted.

Comparative effectiveness

6.10 The results from the ITT population of the EXTREME trial, unchanged from the March 2016 submission, are summarised in Table 6.

Table 6: Summary of outcomes in the EXTREME trial

	Cetuximab + CT ^a n/N (%)	CT only ^b n/N (%)	Absolute difference	HR (95% CI)	Log-rank p- value (stratified)
Overall survival					
No. of deaths	167/222 (75.2)	176/220 (80.0)	-	NR	NR
Median months OS (95% CI)	10.1 (8.6, 11.2)	7.4 (6.4, 8.3)	2.7	0.797 (0.644,0.986)	0.036
Progression-free survival					
No. progressed	168/222 (75.7)	173/220 (78.6)	-	NR	NR
Median PFS months (95% CI)	5.6 (5.0, 6.0)	3.3 (2.9, 4.3)	2.3	0.538 (0.431,0.672)	<0.0001
				OR(95%CI)	CMH P-value
Best overall response^c	79/222 (35.6)	43/220 (19.5)	16.1%	2.326 (1.504, 3.600)	0.0001
Complete response	15/222 (6.8)	2/220 (0.9)	5.9%	NR	NR
Partial response	64/222 (28.8)	41/220 (18.6)	10.2%	NR	NR

Abbreviations: NR = not reported, OR=odds ratio, HR=hazard ratio, CMH = Cochran-Mantel-Haenszel test (stratified by previous CT and by KPS)

^a follow up 19.1 months

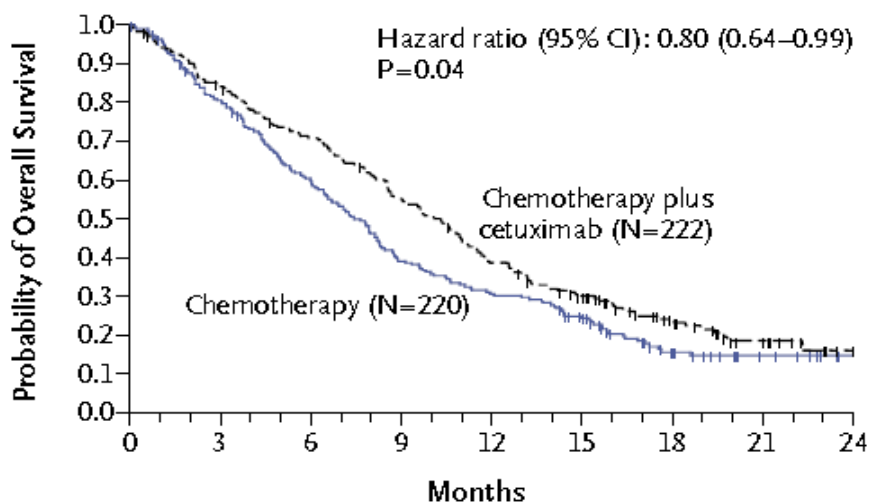
^b follow up 18.2 months

^c defined as number of patients with complete or partial response persisting for at least 4 weeks

Source: Table 2.5.1, p55, Table 2.5.2, p56 and Table 2.5.3, p58 of the resubmission.

6.11 Kaplan Meier estimates for OS and PFS from the EXTREME trial, unchanged from the previous submission, are presented in Figures 1 and 2 respectively.

Figure 1: Kaplan Meier Estimates of overall survival for the EXTREME ITT population

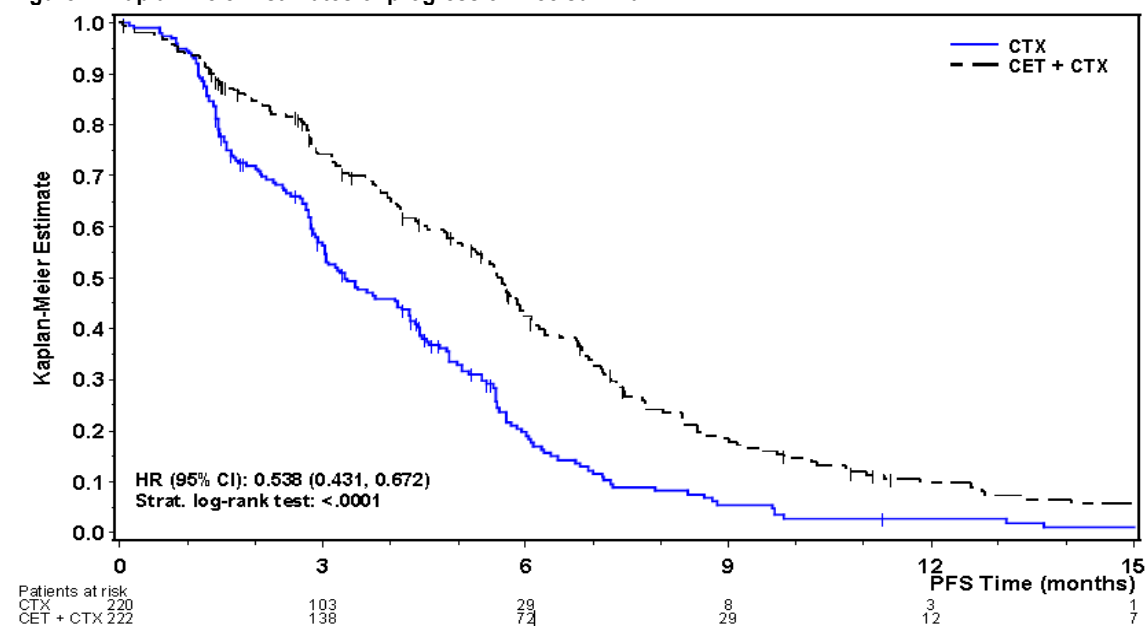


No. at Risk									
Chemotherapy	220	173	127	83	65	47	19	8	1
Chemotherapy plus cetuximab	222	184	153	118	82	57	30	15	3

ITT = Intention to Treat

Source: Figure 2.5.1, p55 of the resubmission

Figure 2: Kaplan Meier Estimates of progression free survival in EXTREME



ITT = Intention to Treat; CT = Chemotherapy; CET = cetuximab; HR = Hazard Ratio; PFS = progression free survival
Source: Figure 2.5.2, p57 of the resubmission

- 6.12 Quality of life (QoL) outcomes in EXTREME were measured using the Quality of Life Questionnaire Core 30 (QLQ-C30⁴) and a head and neck module with 35 questions (QLQ-H&N35). Of particular interest is the results of the QLQ-C30, which were converted into EQ-5D scores using a crosswalk algorithm originally designed for pancreatic cancer, the converted utility values were reported in Greenhalgh et al 2008 and were applied in the economic evaluation. The algorithm uses only responses to 6 of the 30 questions from the QLQ-C30 to estimate the EQ-5D.
- 6.13 Detailed per item QLQ-C30 responses were not reported in the resubmission. The reported summary scores indicated that although participants in the cetuximab + CT treatment arm reported higher mean scores over a six-month period compared to patients in the CT only treatment group, the mean differences were numerically small and not statistically significant with wide confidence intervals.
- 6.14 Based on the conversion by Greenhalgh et al 2008, patients in the PF health state treated with cetuximab + CT had a higher QoL versus those treated with CT only (0.69 vs 0.65). These differential utilities were then applied in the modelled economic evaluation. The ESC advised that this was not appropriate, as:

⁴ The QLQ-C30 is a cancer specific self-administered survey with 30 questions, comprising an overall global health status/QoL scale, five functional scales (physical, role, emotional, cognitive, and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain) and six single-item symptom scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). Only 6 items (out of 30) were used in the cross walk algorithm to derive the health state utilities (i.e., overall health, ability to take a short walk, self-care, sleeping, concentration and family life).

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- There was no statistically significant difference between cetuximab + CT and CT only treatment arms for the QLQ-C30;
- only 44% of patients had both an evaluable baseline and a post-baseline assessment in the EXTREME trial; and
- QoL responses may have been biased due to the open label nature of the trial.

6.15 In the QLQ-H&N35, the addition of cetuximab to CT improved the scores for pain (p=0.0083), swallowing (p=0.0034), speech problems (p=0.0029) and social eating (p=0.0182) at the Cycle 3 assessment after adjusting for differences at baseline. There were no significant differences in the outcomes for other items.

Meta-analyses (anti-EGFR antibodies)

6.16 The ESC and PBAC noted that the resubmission presented a meta-analysis of the EXTREME and SPECTRUM (another trial identified for other anti-EGFR antibodies in first line treatment of RM SCCHN trials), following previous PBAC advice (cetuximab March 2016 PSD, 7.7).

6.17 The ESC noted that PARTNER was excluded from the primary meta-analysis by the resubmission as patients in the CT only treatment arm could cross over and receive panitumumab after progression whereas in the EXTREME and SPECTRUM trials crossover was not explicitly permitted even though a proportion of patients treated with CT only (6.4%) in EXTREME were treated with cetuximab after progression. The PBAC considered that exclusion of the PARTNER trial from the primary meta-analysis was appropriate given these differences. Results of both analyses are summarised in Table 7.

Table 7: Results of the pooled analysis of EXTREME, SPECTRUM and PARTNER

Overall Survival, median months (95%CI)				Hazard Ratio
Trials	N	Anti-EGFR antibody ^a , N	CT only, N	
EXTREME	442	10.1 (8.6, 11.2), N=222	7.4 (6.4, 8.3), N=220	0.80 (0.64, 0.99)
SPECTRUM	657	11.1 (9.8, 12.2), N=327	9.0 (8.1, 11.2), N=330	0.87 (0.73, 1.05)
PARTNER	103 ^b	12.9 (9.4, 18.5), N=52	13.8 (11.8, 22.9), N=51	1.10 (0.71, 1.72)
Pooled (EXTREME + SPECTRUM), I²=0%; p=0.02				0.84 (0.73, 0.97)
Pooled (EXTREME + SPECTRUM+ PARTNER), I²=0%; p=0.03				0.86 (0.76, 0.99)
Progression Free Survival, median months(95%CI)				
EXTREME	442	5.6 (5.0, 6.0), N=222	3.3 (2.9, 4.3), N=220	0.54 (0.43, 0.67)
SPECTRUM	657	5.8 (5.6, 6.6), N=327	4.6 (4.1, 5.4), N=330	0.78 (0.66, 0.92)
PARTNER	103 ^b	6.9 (4.7, 8.3), N=52	5.5 (4.1,6.8), N=51	0.63 (0.40, 1.00)
Pooled (EXTREME + SPECTRUM), I²=85%; p=0.02				0.65 (0.64, 0.94)
Pooled (EXTREME + SPECTRUM+ PARTNER), I²=71%; p=0.002				0.65 (0.49, 0.85)
Best overall response, proportion (95%CI) ^c				Odds Ratio
EXTREME	442	35.6% (29.3,42.3), N=222	19.5% (14.5,25.4), N=220	2.27 (1.48, 3.50)
SPECTRUM	566 [^]	36% (31,42), N=278 [^]	25%(20,31), N =288 [^]	1.68 (1.17, 2.41)
Pooled EGFR inhibitor, I²=10%; p<0.0001				1.91 (1.42, 2.56)

Abbreviations: CI = confidence interval, EGFR = Epithelial Growth Factor Receptor inhibitor, CT = chemotherapy
 Source: Figures 2.6.2, 2.6.4 and 2.6.6, pp82-83 of the resubmission, Vermorken 2008 and Vermorken 2013

- 6.18 Neither of the panitumumab trials reported statistically significant differences in OS between patients treated with panitumumab + CT and CT only. This may be attributed to the higher OS observed in the CT only arm in SPECTRUM compared to EXTREME (point estimate for median of 9.0 months vs 7.4 months) and significant crossover from the CT only arm to the panitumumab treatment arm (55%) in PARTNER which confounded the OS results. Patients in the CT only arm in PARTNER had a longer median OS (13.8 months; CI: 11.8, 22.9) than patients in the panitumumab + CT arm (12.9 months; CI: 9.4, 18.5).
- 6.19 The pooled anti-EGFR antibody trials in RM SCCHN showed statistically significant differences in the outcomes of OS, PFS and best overall response in patients treated with anti-EGFR antibodies + CT compared to CT only. However, the clinical significance of the results remains uncertain. The pooled results indicated a smaller incremental benefit compared to the results of the EXTREME trial. The PBAC noted that the difference in OS for patients in the CT alone arm for the EXTREME and SPECTRUM trials and considered that this complicated interpretation of the meta-analysis results. Overall, the PBAC considered that the EXTREME trial may present the most favourable results for the EGFR + CT combination in patients with RM SCCHN.

Comparative harms

- 6.20 Adverse events which were statistically significantly ($p \leq 0.05$) different between treatment arms in EXTREME are summarised in Table 8 below. These results had previously been presented in the March 2016 submission; however, additional statistical comparisons were conducted during the evaluation of this submission.

Table 8: Summary of statistically significant adverse events in the EXTREME trial

Trial ID	Cetuximab + CT (n= 219) n(%)	CT only (n=215) n(%)	RD (95% CI)
Any AE	218 (99.5)	208 (96.7)	0.03 (0.003, 0.05)
AE leading to discontinuation of treatment	66 (30.1)	38 (17.7)	0.12 (0.05, 0.20)
Any grade 3 or 4 AE	179 (81.7)	164 (76.3)	0.05 (-0.02, 1.31)
AE leading to death	34 (15.5)	33 (15.3)	0.002 (-0.67, 0.07)
Anaemia (any)	93 (42.5)	114 (53.0)	-0.11 (-0.20, -0.12)
Rash			
-Any	61 (27.9)	4 (1.9)	0.26 (0.2, 0.33)
-Grade 3/4	11 (5.0)	0 (0)	0.05 (0.03, 0.09)
Diarrhoea (any)	57 (26.0)	35 (16.3)	0.10 (0.02, 0.17)
Anorexia			
-Any	55 (25.1)	31 (14.4)	0.11 (0.03, 0.18)
-Grade 3/4	11 (5.0)	3 (1.5)	0.04 (0.003, 0.08)
Pyrexia (any)	49 (22.4)	28 (13.0)	0.09 (0.02, 0.17)
Acne (any)	48 (21.9)	0	0.22 (0.17, 0.28)
Dermatitis acneiform (any)	32 (14.6)	0	0.15 (0.11, 0.20)
Dry skin	30 (13.7)	1 (0.5)	0.13 (0.09, 0.19)
Hypocalcaemia			
-Any	27 (12.3)	10 (4.7)	0.08 (0.03, 0.13)
-Grade 3/4	9 (4.1)	2 (0.9)	0.03 (0.003, 0.07)
Hypomagnesaemia			
-Any	24 (11.0)	11 (5.1)	0.06 (0.007, 0.11)
-Grade 3/4	11 (5.0)	3 (1.4)	0.04 (0.003, 0.08)
Sepsis (including septic shock), Grade 3/4	9 (4.1)	1 (0.5)	0.04 (0.01, 0.08)

RD results of statistical comparisons conducted during the evaluation statsdirect v3.1.11

Abbreviations: AE = adverse event; CT = chemotherapy; NR = not reported, RD = Risk difference

^a AEs reported in ≥10% of subjects or Grade 3 or 4 AEs reported in ≥5% of subjects in either group. NR values for Grade 3 or 4 were values < 5%, and not included in the main body of the trial report (appendices not provided in the resubmission).

Source: Tables 2.5.12, p69; table 2.5.14, p71 table 2.5.15 ,p72 and table 2.5.17, p74 of the resubmission, Table 12.12; p128 of the trial report; Vermorken 2008

- 6.21 There were statistically significantly more patients treated with cetuximab + CT who experienced rash, diarrhoea, anorexia, pyrexia, acne, dermatitis acneiform, dry skin, hypocalcaemia and hypomagnesaemia in patients treated with cetuximab + CT, compared to patients those treated with CT only.
- 6.22 In terms of grade 3 and 4 adverse events, there were also statistically significantly more patients who experienced rash, anorexia, hypocalcaemia and hypomagnesaemia events for those treated with cetuximab +CT compared with patients treated with CT only.
- 6.23 The PBAC had previously considered that the addition of cetuximab to platinum-based chemotherapy is inferior to platinum-based chemotherapy alone in terms of comparative safety (cetuximab March 2016 public summary document (PSD) 7.6).

Benefits/harms

- 6.24 The relative benefits and harms for cetuximab + CT compared to CT only reported in the EXTREME trial are summarised in Table 9.

Table 9: Summary of comparative benefits and harms for cetuximab + CT and CT only

Trial	Cetuximab + CT n/N	CT only n/N	OR (95% CI)	Event rate/100 patients ^a		RD (95% CI)
				Cetuximab + CT	CT only	
Benefits						
Proportion of best overall response^b						
EXTREME	79/222	43/220	2.326 (1.504, 3.60)	35.6	19.5	0.16 (0.08, 0.24)
Overall Survival						
EXTREME	Cet + CT	CT only	Absolute difference	HR (95% CI)		
Deaths* n/N (%)	167/222 (75.2)	176/220 (80.0)	4.8	NR		
Median months (95%CI)	10.1 (8.6, 11.2)	7.4 (6.4, 8.3)	2.7	0.797 (0.644, 0.986)		
Progression free survival						
EXTREME	Cet + CT	CT only	Absolute difference	HR (95% CI)		
No progressed* n/N (%)	168/222 (75.7)	173/220 (78.6)	2.9	NR		
Median months (95%CI)	5.6 (5.0, 6.0)	3.3 (2.9, 4.3)	2.3	0.538 (0.431, 0.672)		
Harms						
EXTREME	Cet + CT n/N	CT only n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Cet + CT	CT only	
Anaemia (any)	93/219	114/215	0.80 (0.66, 0.98)	42.5	53.0	-0.11(-0.20, -0.12)
Rash						
-Any	61/219	4/215	15.0 (5.8, 39)	27.9	1.9	0.26 (0.2, 0.33)
-Grade 3 or 4	11/219	0/215	22.8 (2.85, inf)	5.0	0	0.05 (0.03, 0.09)
Diarrhoea (any)	57/219	35/215	1.60 (1.10, 2.33)	26.0	16.3	0.10 (0.02, 0.17)
Anorexia						
-Any	55/219	31/215	1.74 (1.18, 2.59)	25.1	14.4	0.11 (0.03, 0.18)
-Grade 3 or 4	11/219	3/215	3.60 (1.10, 11.88)	5	1.5	0.04 (0.003, 0.08)
Pyrexia (any)	49/219	28/218	1.72 (1.13, 2.63)	22.4	13.0	0.09 (0.02, 0.17)
Acne (any)	48/219	0/215	96.12 (12.47, inf)	21.9	0	0.22 (0.17, 0.28)
Dermatitis acneiform (any)	32/219	0/215	64.62 (8.31, inf)	14.6	0	0.15 (0.11, 0.20)
Dry skin	30/219	1/215	29.45 (5.18, 170.1)	13.7	0.5	0.13 (0.09, 0.19)
Hypocalcaemia						
-Any	27/219	10/215	2.65 (1.34, 5.29)	12.3	4.7	0.08 (0.03, 0.13)
-Grade 3 or 4	9/219	2/215	4.42 (1.09, 18.01)	4.1	0.9	0.03 (0.003, 0.07)
Hypomagnesaemia						
-Any	24/219	11/215	2.14 (1.09, 4.22)	11.0	5.1	0.06 (0.007, 0.11)
-Grade 3 or 4	11/219	3/215	3.60 (1.10, 11.88)	5.0	1.4	0.04 (0.003, 0.08)
Sepsis (including septic shock), Grade 3 or 4	9/219	1/215	8.84 (1.47, 53.73)	4.1	0.5	0.04 (0.01, 0.08)

Italic indicates results of statistical comparisons conducted during the evaluation StatsDirect V3.1.11. Text in bold indicate statistically significant difference

Abbreviations: Cet=cetuximab, CT = chemotherapy; RD = risk difference; RR = risk ratio; inf = infinite.

^a Median duration of follow-up: cetuximab + CT 19.1 months, CT only 18.2 months

^b defined as number of patients with complete or partial response persisting for at least 4 weeks

Source: Tables 2.5.12, p69; table 2.5.14, p71 table 2.5.15 ,p72 and table 2.5.17, p74 of the resubmission, Table 12.12; p128 of the trial report; Vermorken 2008

6.25 On the basis of direct evidence presented by the resubmission, treatment with cetuximab + CT compared with CT only resulted in a statistically significant increase in overall survival (median of approximately 2.7 months) and progression free survival (median of approximately 2.3 months).

6.26 On the basis of direct evidence presented in the resubmission, for every 100 patients treated with cetuximab + CT in comparison to CT only over a median duration of

follow-up of 19.1 months for patients treated with cetuximab + CT and 18.2 months for CT only, approximately:

- 16 additional patients would have a complete or partial response for at least 4 weeks;
- 26 additional patients would experience any rash and 5 additional patients would experience Grade 3 or 4 rash;
- 10 additional patients would experience diarrhoea;
- 11 additional patients would experience any anorexia and 4 additional patients would experience Grade 3 or 4 anorexia;
- 9 additional patients would experience pyrexia;
- 22 additional patients would experience any acne;
- 15 additional patients would experience dermatitis acneiform;
- 26 additional patients would experience dry skin;
- 8 additional patients would experience any hypocalcaemia and 3 additional patients would experience Grade 3 or 4 hypocalcaemia;
- 6 additional patients would experience any hypomagnesaemia and 4 additional patients would experience Grade 3 or 4 hypomagnesaemia; and
- 4 additional sepsis events (including septic shock), however
- 11 fewer patients would experience anaemia.

Clinical claim

- 6.27 The resubmission claimed that cetuximab in combination with platinum based CT for the treatment of RM SCCHN was superior in terms of effectiveness and inferior in terms of safety compared with platinum based CT only. The resubmission described the safety profile of cetuximab as ‘manageable’.
- 6.28 The PBAC previously considered that the claim of superior comparative effectiveness was reasonable for the ITT population with respect to overall survival, progression-free survival and response rates, although the magnitude of the benefit was small (cetuximab March 2016 PSD 7.5).
- 6.29 The PBAC also previously considered that the addition of cetuximab to platinum-based chemotherapy is inferior to platinum-based chemotherapy alone in terms of comparative safety for the ITT population, but the adverse event profile to cetuximab is widely known and well managed (cetuximab March 2016 PSD 7.6).
- 6.30 The PBAC agreed with ESC that although the resubmission appropriately presented evidence for the ITT population and a meta-analysis with other anti-EGFR antibodies, there was no compelling evidence provided in the resubmission that should necessitate any change to PBAC’s previous conclusions about the clinical claim.

Economic analysis

- 6.31 The resubmission presented a stepped economic evaluation including a trial-based cost per additional responder analysis based on results of the EXTREME trial,

followed by an extrapolated modelled economic evaluation using partition survival analysis. The modelled structure was unchanged from the March 2016 submission, however previously it was referred to as an area under the curve (AUC) analysis. Time to event data (OS and PFS) from EXTREME were applied for the first 12 months for PFS and 18.7 months for OS. After 12 and 18.7 months, PFS and OS were extrapolated to five years using log logistic parametric distributions.

- 6.32 The main differences versus the March 2016 submission were: i) the resubmission updated the modelled population to reflect the more appropriate ITT population and ii) the resubmission nominated Greenhalgh et al 2008 for source of health state utilities. A summary of the model structure and rationale is presented in Table 10.

Table 10: Summary of model structure and rationale

Component	Summary
Type of analysis	The submission presented a partitioned survival analysis. Time to event data (OS and PFS) from EXTREME was applied for the first 12 months for PFS and 18.7 months for OS. After 12 and 18.7 months, PFS and OS were extrapolated to five years in both arms using log logistic parametric distributions.
Time horizon	Five year in the model base case versus a median follow up of 19.1 and 18.2 months respectively in the cetuximab+ CT and CT only arms of the EXTREME trial. The time horizon was unchanged from the previous submission. The PBAC had previously considered a five-year time horizon to be optimistic. The model was sensitive to the time horizon.
Outcomes	Responder, life year gained and QALY gained.
Methods used to generate results	Partition survival analysis, using time to event data from the EXTREME trial plus parametric extrapolation to 5 years. AUC analysis were then undertaken to estimate accumulated life years with and without disease progression. Progressed disease was estimated as the difference between OS and PFS. QALYs were then estimated by applying health state utility values from Greenhalgh et al 2008 which reported the results of the submission to NICE. The ESC had previously expressed concerns that utilities reported in Paleri 2008 (used in the March 2016 model) were not robust since the health state utilities in Paleri 2008 were obtained from a consensus of two UK clinicians for good and poor symptom control with palliative care. Model structure was identical to the March 2016 submission.
Extrapolation	Time to event data (OS and PFS) from EXTREME was applied for the first 12 months for PFS and 18.7 months for OS. After 12 and 18.7 months, PFS and OS were extrapolated to five years using log logistic parametric distributions. The extrapolation function was chosen among six possible parametric functions (exponential, Weibull, log logistic, log normal, Gamma and Gompertz). The previous submission had also used the log logistic function to extrapolate time to event data for the ITT population.

Abbreviations: CT = chemotherapy, QALY = quality adjusted life year, AUC = area under curve, OS = overall survival, PFS = progression free survival, NICE = National institute for Health and Care Excellence

Source: Table 3.1.1, p91 of the resubmission

- 6.33 The key drivers of the modelled economic evaluation are summarised in Table 11.

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Table 11: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	The method used to extrapolate time to event data had a significant impact on the ICER. Results of extrapolations conducted during the evaluation using alternate parametric survival functions illustrated that while most curves appeared to follow the Kaplan-Meier trial-based curves, their extrapolated estimates varied greatly. The reported AIC values were also similar across several parametric functions with no function having a clear superior fit. Compared with Weibull extrapolation which was used in the model evaluated by NICE, extrapolation using the log logistic function allowed individuals to prolong time spent in their current health state, with an elongated tail (see Figure 3 below). This significantly favoured cetuximab + CT, since a higher proportion of individuals were in PFS and OS at the truncation point of the Kaplan Meier curves, an elongated tail in the survival function would ensure more benefit would accrue to patient in the cetuximab + CT arm over time compared to CT only.	High, favoured cetuximab
Utilities	Different to the previous submission, which used utility values reported by Paleri 2008, health state utilities applied in the model were obtained from Greenhalgh et al 2008. These utilities were estimated from results of the QLQ-C30 questionnaire in the EXTREME trial via a cross-walk algorithm converting them to EQ-5D utility values. A higher mean utility value was estimated for patients in the cetuximab + CT arm of the model (0.69) compared to CT only (0.65) in the PF health state. The ESC considered that this was not appropriate and was not conservative. There were no statistically significant differences between the two treatment groups in summary QLQ-C30 scores, the estimated utility values also had wide confidence intervals and were not significantly different. The model was sensitive to the assumption of differential utilities for the PF health state. By contrast in the PD health state, the same health state utility was more appropriately applied (0.52) irrespective of treatment assignment.	Moderate, favours cetuximab
Time horizon	As for the previous submission, a five-year time horizon was chosen for the base case. The resubmission justified this choice by claiming that lifetime models were more common in RM SCCHN in identified publications, and the PBAC had previously accepted five-year time horizons for metastatic prostate cancer (abiraterone July 2012) and non-small cell lung carcinoma (nivolumab March 2017). It was noted that the median overall survival reported in these two considerations were notably longer than the median overall survival reported in the EXTREME trial. The ICER was sensitive to assumptions around time horizon, however the magnitude of the effect was significantly less than the impact of the choice of extrapolation. While the ICER decreases substantially beyond a 1 year time horizon it stabilised by 3.5 years, in contrast, differences due to extrapolation function used persisted well beyond 5 years (see Figure 4).	Moderate, favours cetuximab
Assumed cetuximab doses	The resubmission assumed that the subsequent dose of cetuximab is 400 mg weekly, based on the mean dose of cetuximab used in the EXTREME trial (406 mg). However, applying the mean body surface area of 1.75 m ² from the EXTREME trial to the recommended cetuximab dose of 250 mg/m ² , a dose of 432.5 mg is estimated, which would require 500 mg of cetuximab under the efficient funding of chemotherapy scheme. The previous submission used mean doses from the oral cavity population instead of the ITT population.	Moderate, favours cetuximab
Method used to assign costs	As for the previous submission, with the exception of palliative care costs which are assigned as patients die in the model, all other expected costs (drug, administration, treatment for adverse events, treatment post progression) are applied on the first day in the model. This is generally not considered to be the appropriate methodology to capture continuing treatment costs. An alternative approach that applied cost over time was therefore conducted during the evaluation. The alternate approach would also permit the testing of a scenario which assumed that all patients receive cetuximab as long as they remain PF. The approach adopted by the resubmission using average treatment costs from the EXTREME trial would have incorporated reduced doses and costs due to some patients not receiving treatments for adverse events in the PF state in the EXTREME trial.	High, favours cetuximab

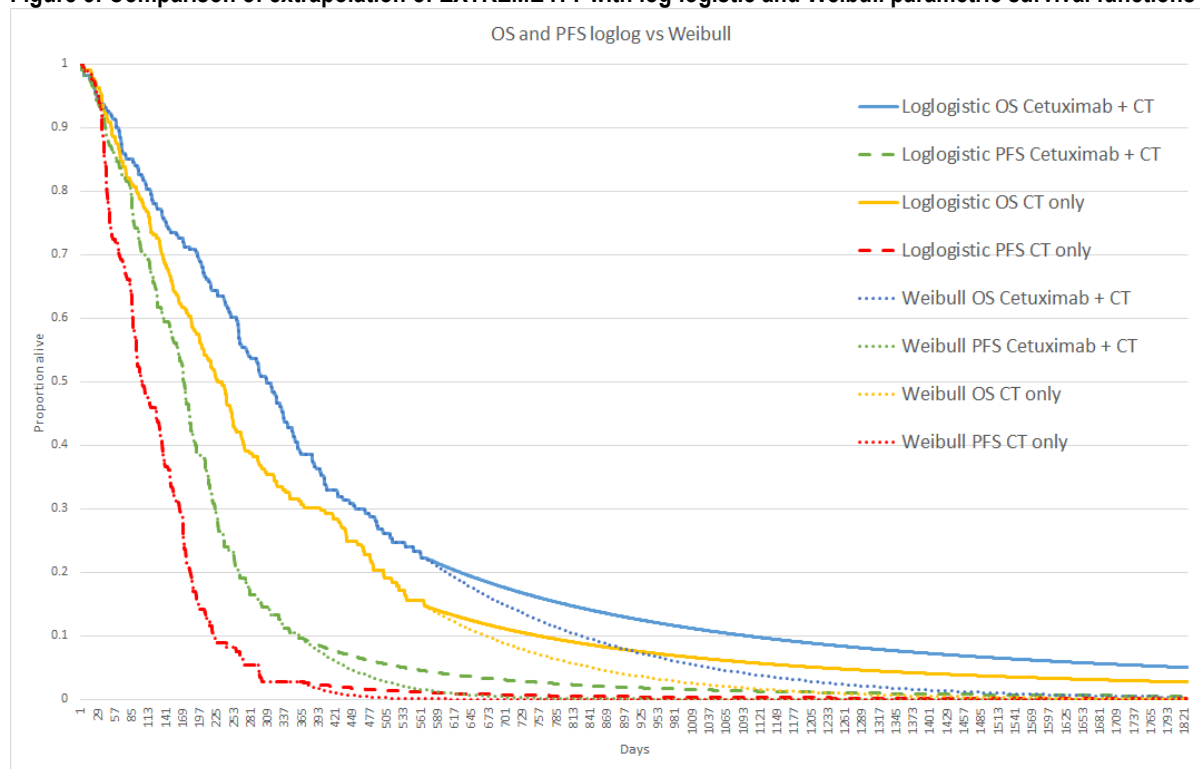
Abbreviations: ICER = incremental cost effectiveness ratio, AIC = Aikake Information Criterion, NICE = National institute for Health and

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Care Excellence, CT = chemotherapy, QALY = quality adjusted life year, OS = overall survival, PFS = progression free survival, QLQ-C30 = Quality of Life Questionnaire Core 30, EQ-5D = EuroQol five dimensions, PF = 'free from progression', PD = "progressed", RM = recurrent or metastatic, SCCHN = squamous cell carcinoma of the head and neck, ITT = intention to treat

Source: Table 3.9.1, p119 of the resubmission and additional sensitivity analysis conducted during evaluation using Attachment 8 Economic Evaluation to the resubmission

Figure 3: Comparison of extrapolation of EXTREME ITT with log logistic and Weibull parametric survival functions



Abbreviations: OS=overall survival, PFS=progression free survival, CT = Chemotherapy

Source: constructed during evaluation using data from Attachment 3b and Attachment 8 of resubmission

6.34 The results of the stepped economic evaluation are presented in Table 12.

Table 12: Results of the stepped economic evaluation

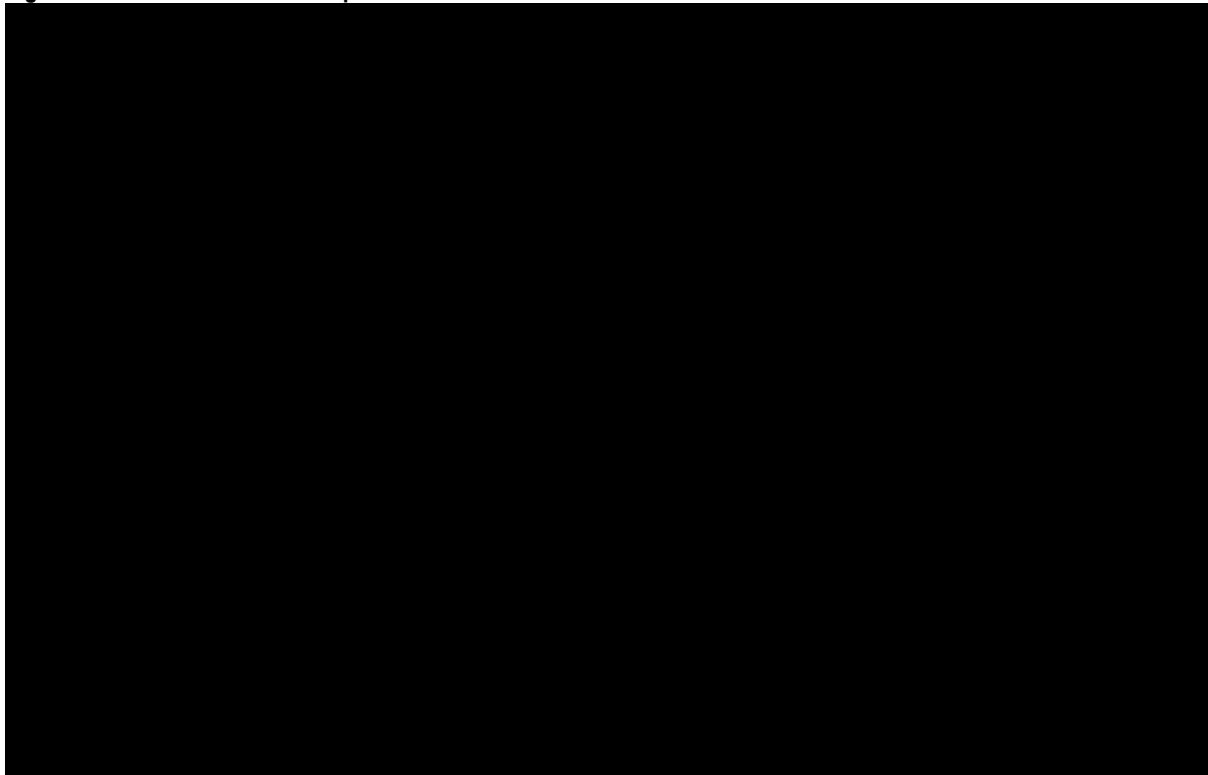
Step and component	Cetuximab + CT	CT only	Increment
Step 1: trial-based costs and responders (trial duration 19.1 months median follow up in cetuximab + CT and 18.2 months in CT only)			
Costs	\$ [REDACTED]	\$1,480	\$ [REDACTED]
Percentage of responders	35.6%	19.5%	16.1%
Incremental cost per additional responder gained			
Step 2: Extrapolated life year gain (5 year time horizon)			
Costs	\$ [REDACTED]	\$12,233	\$ [REDACTED]
Life years gain	1.173	0.925	0.248
Incremental cost per additional life year gained			
Step 2: Extrapolated QALY gain (5 year time horizon)			
Costs	\$ [REDACTED]	\$12,233	\$ [REDACTED]
QALY	0.705	0.527	0.178
Incremental cost per QALY gained			
\$ [REDACTED]			

CT = chemotherapy

Source: Tables 3.8.4 and 3.8.5, p118 of the resubmission

- 6.35 The ICER for the ITT population in the previous submission was \$105,000/QALY - \$200,000/QALY (incremental cost \$15,000 - \$45,000, incremental QALY gain 0.190). The decrease in base case ICER in this resubmission was mainly due to a lower incremental cost driven by the increase in confidential rebate resulting in a lower effective price, and a lower dose cap for cetuximab. Additionally, the revised economic model included lower assumed administration costs and higher assumed palliative cost (which was disproportionately applied to the CT only arm). The resubmission also reported a lower QALY increment which was the result of using utilities reported in Greenhalgh et al 2008 instead of Paleri 2008.
- 6.36 The incremental QALY gain reported in the resubmission for cetuximab + CT over CT only was significantly higher than comparable published models which specifically investigated the addition of cetuximab to platinum based CT in RM SCCHN. The resubmission's estimate of 0.178 QALY gain over five years was almost double that reported in Hannouf et al 2012 (0.093 over 3 years) or 25% higher than Greenhalgh et al 2008 (of 0.142 over a lifetime).
- 6.37 Favourable assumptions (including but not limited to assumed cetuximab doses, method to assign costs and estimated administration costs) potentially resulted in the lower ICER estimated. Figure 4, constructed during the evaluation illustrates the impact of varying both parametric survival function used to extrapolate PFS and OS and the time horizon on the estimated ICER.

Figure 4: ICER for different extrapolation methods over different time horizons



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Source: constructed during evaluation using parameters in Attachment 3b and Attachment 8 of the resubmission

- 6.38 As illustrated in Figure 4, the choice of the functional form for extrapolation had a significant impact on the resultant ICER, mainly via variations in the estimated survival and QALY gain in the cetuximab + CT arm after 1 year for PFS and 18.7 months for OS. The expected costs did not change considerably, as all expected drug, administration and adverse event costs were assigned upfront, with the only variation of cost over time was palliative costs.
- The difference in ICER at 5 years between the most optimistic and the most pessimistic curves was \$15,000/QALY - \$45,000/QALY. Assuming the Weibull functional form, which was nominated as the best fit in Greenhalgh et al 2008 and had similar visual fit and AIC as the log logistic function, resulted in an increase in the ICER by 25% to \$45,000/QALY - \$75,000/QALY from a base case of \$45,000/QALY - \$75,000/QALY. When the Gamma function was adopted, the ICER was found to increase further to \$75,000/QALY - \$105,000/QALY over 5 years. Given that the resubmission did not provide a strong justification for why the log logistic function should be chosen over other functional forms, the ICER was considered by ESC to be highly uncertain.
 - The ESC considered that the Weibull or the Gompertz function would be the most appropriate method of extrapolation based on visual inspection, while the gamma function would be the more appropriate method based on the AIC values provided in the submission. The Pre-Sub-Committee Response (PSCR) stated that the gamma function should be excluded from consideration as the OS curve for CT alone crosses above the OS curve for cetuximab. Given there was no plausible rationale for cetuximab patients to die substantially faster than patients on CT alone, the PSCR contended that the curves generated by the gamma function were not clinically meaningful.
 - The ESC was concerned that the AIC value provided in the submission for the Gompertz function was disproportionately high compared to the other functions. In the pre-PBAC response the sponsor advised that with the exception of the Gompertz, the AIC statistics summarised in the Commentary were calculated on logged data, whereas the Gompertz was based on unlogged data. The sponsor noted that when unlogged data are used for all distributions, the AIC for the Gompertz is of a similar magnitude to the other distributions.
- 6.39 The pre-PBAC response identified that based on the AIC, the Weibull and log logistic functions provide the best fit to OS data for cetuximab and chemotherapy arms, respectively, and based on BIC the log logistic provides the best fit for OS in the chemotherapy arm, whilst the exponential provides the best fit for the cetuximab arm. Therefore the sponsor contended that no function has a clearly superior fit overall. The PBAC considered that given this uncertainty the more conservative Weibull curve was most appropriate for the base case.

- 6.40 The PSCR argued that since at least eight patients from the ITT population of EXTREME were alive at five years, a five-year time horizon was data driven and appropriate.
- 6.41 The resubmission assumed that the subsequent dose of cetuximab is 400 mg weekly, based on the mean dose of cetuximab used in the EXTREME trial (406 mg). Given that the recommended dose in the PI is 250 mg/m², assuming a body surface area (BSA) of 1.75 m² would result in a dose of 437.5 mg, which would necessitate 1 × 500 mg vial instead of the 4 × 100 mg assumed in the base case. The PSCR argued that trial-based dosing data showed that fewer milligrams were required per subsequent infusion, and hence 4 × 100 mg vials were sufficient in the ITT population. The ESC disagreed, and advised that a dose of 400 mg of cetuximab would underestimate the actual usage of cetuximab in the proposed setting at the recommended dose. When the subsequent cetuximab dose of 500 mg was applied instead of 400 mg, the ICER increased from \$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$75,000/QALY. In the pre-PBAC response the sponsor indicated that an analysis of individual patient level data demonstrated that 81% of patients would require 1 × 500 mg vial and therefore the revised base case should assume that for subsequent cetuximab infusions, 81% of patients receive 1 × 500 mg vial and the remaining 19% receive 4 × 100 mg vials. The PBAC agreed with the sponsor that these data were appropriate to inform the base case.
- 6.42 The PSCR stated that the addition of cetuximab significantly improved QLQ-H&N35 scores for pain, swallowing, speech problems and social eating. As such the PSCR argued that since these symptoms are highly pertinent to this population, significant improvement in these symptoms supported a higher progression-free utility score for patients treated with cetuximab + CT. The ESC considered that the assumption of differential utilities for patients treated with cetuximab + CT versus CT only in the progression-free health state (utility values of 0.69 and 0.65 respectively) was inappropriate, noting the observed increase in a wide range of AEs, and that only 44% of the questionnaires (across both QLQ-C30 and QLQ-H&N35) had both an evaluable baseline and post-baseline assessment. The PBAC noted that the assumption of differential utility values for the pre-progression state in the two arms increased the uncertainty in the ICER. The consequence of this assumption was a lower ICER than would have been obtained if the PFS utility was held constant irrespective of treatment exposure. Having noted these concerns, the PBAC accepted the differential PFS utilities in the base case analysis given they were sourced from the clinical trial.
- 6.43 The resubmission applied an average treatment cost from the EXTREME trial upfront to each treatment arm rather than allowing costs to accrue over time.
- The ESC considered that the method used in the resubmission to assign costs in the model was inappropriate. The ESC considered that if costs were to be adjusted to allow for time off treatment or time on reduced doses, data should

be presented to show the pattern of time off treatment or time on reduced doses, as patients with treated AEs may recommence treatment at the full dose and remain on full dose until disease progression, especially given that the resubmission had argued that the side effects of cetuximab would be manageable. As such, the ESC considered that applying costs over time and assuming all patients would continue to receive cetuximab in the PF health state would be more appropriate.

- The ESC noted an ICER of \$45,000/QALY - \$75,000/QALY was derived from the sensitivity analysis in which costs were accrued over time compared to a base case of \$45,000/QALY - \$75,000/QALY in the resubmission.
- The pre-PBAC response argued that PFS is not an accurate proxy for time-on-treatment as it does not account for patients who cease treatment early or have treatment interruptions due to AEs or circumstances other than progression. The sponsor noted that in the EXTREME trial the median PFS in the cetuximab arm was 24.3 weeks but a median of only [REDACTED] infusions of cetuximab were received. Therefore the sponsor proposed that the modelled costs should be reduced by a factor of [REDACTED] ($[REDACTED] \div 24.3$) compared to the PFS duration. The PBAC considered that there may be some reduction in the cost from actual time on treatment and that this should be incorporated into the base case, though the Committee noted that the factor is somewhat uncertain as it was crudely determined, unable to be verified and may not be as low as [REDACTED].

6.44 The results of the univariate sensitivity analyses are summarised in Table 13, the results indicate that the model was sensitive to the dose of subsequent cetuximab and its administration costs, the shortening of the time horizon, assumption of differential utility values depending on treatment and the assumption that drug costs are applied upfront rather than incurred over time and assuming all patients receive cetuximab as long as they remain in the PF health state (see also Table 11).

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Table 13: Univariate sensitivity analyses of the resubmission's economic model

Scenario	Incremental Cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	0.178	\$ [REDACTED]
Time horizon 3 years (base case 5 years)	\$ [REDACTED]	0.149	\$ [REDACTED]
Time horizon 10 years (base case 5 years)	\$ [REDACTED]	0.207	\$ [REDACTED]
Assume 1×500mg vial for subsequent cetuximab dosing in cetuximab arm (base case 4×100mg vials)	\$ [REDACTED]	0.178	\$ [REDACTED]
Overall Utilities from Greenhalgh et al 2008 PFS = 0.67, Progressed = 0.52 (base case treatment specific utilities for PFS: PFS Cetuximab = 0.69, PFS CT = 0.65, Progressed = 0.52)	\$ [REDACTED]	0.160	\$ [REDACTED]
Assume patients receiving infusions in public hospitals (50.2%) incur additional \$200.33 per infusion based on IHPA cost for non-admitted patients treated in public hospital for chemotherapy treatment (base case: not considered)	\$ [REDACTED]	0.178	\$ [REDACTED]
Assume infusion cost is same as previous submission (\$ [REDACTED]) (base case \$97.95 for cetuximab ± CT and \$65.05 for cetuximab monotherapy)	\$ [REDACTED]	0.178	\$ [REDACTED]
Assume that all costs are incurred over time [^] (base case: all expected costs except for palliative costs were incurred at the start of model)	\$ [REDACTED]	0.178	\$ [REDACTED]

Abbreviations: ICER = Incremental Cost Effectiveness Ratio; CET = cetuximab + chemotherapy arm; CT = chemotherapy only arm; PFS = Progression Free Survival; IHPA = Independent Hospital Pricing Authority

[^] also assuming that all patients receive cetuximab as long as they remain in free from progression (PF) health state

Source: Table 3.9.1, p119 of the resubmission and constructed during evaluation

The redacted table shows ICERs in the range of \$45,000/QALY - \$75,000/QALY.

6.45 The results of a series of multivariate analyses which considered the effects of a combination of the key assumptions identified in the univariate sensitivity analyses are presented in Table 14.

Table 14: Multivariate Sensitivity analyses conducted during the evaluation

Scenario	Incremental Cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	0.178	\$ [REDACTED]
Assume 1×500mg vial for subsequent cetuximab dosing, time horizon of 3 years	\$ [REDACTED]	0.149	\$ [REDACTED]
Assume 1×500mg vial for subsequent cetuximab dosing, extrapolation with Weibull	\$ [REDACTED]	0.146	\$ [REDACTED]
Assume 1×500mg vial for subsequent cetuximab dosing, extrapolation with Weibull, time horizon 3 years	\$ [REDACTED]	0.138	\$ [REDACTED]
Assume extrapolation with Weibull, cost accrued over time [^]	\$ [REDACTED]	0.146	\$ [REDACTED] [^]
Assume 1×500mg vial for subsequent cetuximab dosing, extrapolation with Weibull, cost accrued over time [^]	\$ [REDACTED]	0.146	\$ [REDACTED] [^]
Assume 1×500mg vial for subsequent cetuximab dosing, extrapolation with Weibull, cost accrued over time [^] , time horizon 3 years	\$ [REDACTED]	0.138	\$ [REDACTED] [^]
Assume 1×500mg vial for subsequent cetuximab dosing, extrapolation with Weibull, cost accrued over time [^] , overall utilities from Greenhalgh et al 2008	\$ [REDACTED]	0.129	\$ [REDACTED]

Abbreviations: ICER = Incremental Cost Effectiveness Ratio;

[^] also assuming that all patients receive cetuximab as long as they remain in free from progression (PF) health state

Source: Constructed during evaluation

The redacted table shows ICERs in the range of \$45,000/QALY - \$200,000/QALY.

6.46 The ESC noted that an additional multivariate sensitivity analysis assuming (i)

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1x500 mg vial for subsequent cetuximab dosing; (ii) extrapolation using the Weibull function; (iii) using costs accrued over time; and (iv) equal utility values in both arms for the progression-free state, resulted in an ICER of \$105,000 - \$200,000 per QALY gained. The ESC advised that this was the most realistic ICER based on the evidence presented in the submission.

6.47 The ESC further noted that, keeping all other assumptions the same, using the Gompertz function instead of Weibull in the above multivariate analysis resulted in an ICER of \$105,000 - \$200,000 per QALY gained.

6.48 In the Pre-PBAC response the sponsor proposed a revised net effective price of \$ [redacted] per 100 mg vial, which is a further [redacted] % reduction from the proposed price in the March 2018 resubmission, recognising the remaining areas of economic uncertainty. Table 15 presents the multivariate sensitivity analyses as provided in the pre-PBAC response and with the proposed reduced effective price.

Table 15: Generation of the revised basecase ICER's at net price of \$ [redacted]/100mg vial and \$ [redacted]/100mg

	Submission Price: \$ [redacted]/100mg			Pre-PBAC Price: \$ [redacted]/100mg ^c		
	log logistic	Weibull	Gompertz	log logistic	Weibull	Gompertz
1. ESC proposed multivariate base case (Assuming 1x500mg vial in 100% of subsequent cetuximab infusions, cost accrued over time ^a , overall utilities from Greenhalgh et al 2008)	\$ [redacted] ^b	\$ [redacted] ^b	\$ [redacted] ^b	\$ [redacted]	\$ [redacted]	\$ [redacted]
2. As for 1 but trial based utility values used	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
3. As for 2 but only [redacted] % of patients receive 1x500mg vial for subsequent cetuximab dosing (based on IPD analysis)	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

^a assuming that all patients receive cetuximab as long as they remain in free from progression (PF) health state.

^b note incorrect numbers were reported in the Pre-PBAC response by sponsor (ie, Weibull reported for log logistic and Gompertz for Weibull)

^c not included in pre-PBAC response, ICERs provided by the department of health

The redacted table shows ICERs in the range of \$75,000/QALY - \$200,000/QALY.

6.49 The PBAC considered that the base case ICER initially presented in the resubmission was underestimated due to the factors identified in the commentary and as noted by the ESC. The PBAC considered the base case should incorporate the following assumptions:

- Costs calculated using the accrued cost method, assuming that for subsequent cetuximab infusions, [redacted] % of patients receive 1 x 500 mg vial and the remaining [redacted] % receive 4 x 100 mg vials;
- Differential utilities (trial-based utility values as per submission);
- A 5 year time horizon;
- [redacted] % fortnightly dosing;

- Applying a ratio of [REDACTED]/24.3 ([REDACTED]) to account for not all patients receiving treatment up until the time of progression; and
- Extrapolation using the Weibull function.

6.50 The PBAC noted this corresponded to scenario 3 (with Weibull extrapolation) in Table 15 with the addition of fortnightly dosing in [REDACTED]% of patients and factoring in the ratio of treatment duration to PFS ([REDACTED]). Using the revised price of \$[REDACTED] per vial, the inclusion of fortnightly dosing reduces the ICER from \$75,000/QALY - \$105,000/QALY for scenario 3 to \$75,000/QALY - \$105,000/QALY and the application of the [REDACTED] ratio to account for a treatment-free interval prior to progression reduces the ICER further to \$45,000/QALY - \$75,000/QALY.

Drug cost/patient/course: \$[REDACTED] (based on price proposed in the resubmission)

6.51 Even though cetuximab is intended to be administered until disease progression, the resubmission proposed a cap of [REDACTED] PBS-subsidised cetuximab doses per patient. Therefore, the drug cost/patient/course was calculated based on the mean number of cetuximab doses used per patient ([REDACTED] doses) in the ITT population of the EXTREME trial when a cap of [REDACTED] infusions per patient was applied. It was assumed that 50.2% of all scripts will be dispensed through public hospitals and 49.8% will be dispensed through private hospitals, based on the breakdown of public vs private hospital scripts for cetuximab when used in locally advanced (LA) SCCHN. A dose of 700 mg was assumed for the initial dose in the first week of treatment (effective price of 1 infusion: \$[REDACTED]) and a dose of 400 mg was assumed for subsequent weekly doses ([REDACTED] infusion × \$[REDACTED] = \$[REDACTED]). A more conservative approach of assuming a subsequent dose of 500-mg (effective price per dose \$[REDACTED]) instead of 400 mg resulted in a drug cost/patient/course of \$[REDACTED] (based on the price proposed in the resubmission). This was significantly lower than the drug cost/patient/course for the ITT population reported in the March 2016 submission (\$[REDACTED]) due to the increase in confidential rebate from [REDACTED]% to [REDACTED]% and the cap of [REDACTED] doses per patient.

Estimated PBS usage & financial implications

6.52 This resubmission was not considered by DUSC. An epidemiological approach was undertaken to estimate usage and financial implications.

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Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated						
Number of scripts dispensed ^a						
Total number of vials reimbursed						
Number of 100mg vials (vials/patient) ^b						
Number of 500mg vials (1 vial/patient)						
Total number of vials dispensed						
Number of 100mg vials (vials/patient) ^c						
Number of 500mg vials (vial/patient)						
Estimated financial implications of cetuximab						
Cost to PBS/RPBS ^d	\$	\$	\$	\$	\$	\$
Co-payments (\$19.29x2/patient) ^e	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
Estimated financial implications for other medications						
Costs of managing AEs (\$22.05/patient) ^f	\$	\$	\$	\$	\$	\$
Incremental cost of CT (\$154.37/patient) ^g	\$	\$	\$	\$	\$	\$
Total cost of other drugs	\$	\$	\$	\$	\$	\$
Total cetuximab + cost of other drugs	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost to the PBS/RPBS	\$	\$	\$	\$	\$	\$
Cost to MBS: Total cost of infusions (Additional \$ /patient)	\$	\$	\$	\$	\$	\$
Net cost to government budget	\$	\$	\$	\$	\$	\$

^a Average number was 20.1 in EXTREME, but resubmission assumed that % of patients will be dosed fortnightly instead of weekly therefore the average for each patient was 17.1 scripts.

^b Number of subsequent infusions = , assuming cap at doses and each patient receiving 4 x 100mg vial per dose

^c Number of subsequent infusions = , assuming % of the 20.1 infusions in EXTREME were given fortnightly instead. However, fortnightly dosing should not reduce the number of vials dispensed, only the number of dispensings. The number of subsequent infusions should be 19.1.

^d Number of patients treated multiplied by \$ (1 Initial infusion at \$ + subsequent infusions at \$ each)

^e The resubmission assumed that 2 co-payments (1 for initial and 1 for subsequent) will be paid per patient.

^f Includes weighted cost for PBS listed therapies for treatment of skin reactions and premedication with prednisolone

^g In EXTREME, patients treated with cetuximab + CT used more doses of CT than patients treated with CT alone.

Source: Attachment 9 Section 4 November 2017 Resubmission final.xls

The redacted table shows that at Year 5 the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

6.53 The previous submission estimated a cost of less than \$10 million in Year 1, increasing to \$10 - \$20 million by Year 5 with a cumulative total of \$30 - \$60 million over the first 5 years of listing based on effective prices (\$ and \$ for 100 mg and 500 mg vials respectively) with a % rebate. The resubmission claimed that despite the expansion of the patient population, the net financial impact was relatively unchanged due to the higher rebate and a cap of infusions per patient proposed. The increased rebate and the cap were not the only factors which led to a lower financial estimate. The resubmission also changed a number of assumptions which reduced the financial estimates from the previous submission including: (i) lower proportion of head and neck cancers within squamous cell carcinomas (90% instead of 100%); (ii) lower proportion of recurrent or metastatic disease (60% instead of 70%); (iii) fewer patients suitable for cetuximab treatment

(60% instead of 75%); (iv) lower subsequent cetuximab doses (400 mg instead of 500 mg); and (v) significantly lower infusion costs per patient (\$ [REDACTED] instead of \$ [REDACTED] per patient due to exclusion of cost for non-admitted chemotherapy treatment costs for public hospitals).

- 6.54 Compared to the previous submission, usage outside of the requested restriction is unlikely due to the expansion of the requested restriction to the whole trial population.
- 6.55 At year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.
- 6.56 The commentary considered the financial impacts presented in the resubmission for the listing of cetuximab on the PBS are likely to be underestimates. When considering a plausible scenario in which i) patients use 500 mg for subsequent dosing, ii) an increased uptake of [REDACTED]% per year (from base case assumptions of year 1 at [REDACTED]% to year 6 at [REDACTED]% to year 1 at [REDACTED]% to year 6 at [REDACTED]%) and iii) non-admitted chemotherapy costs for public hospitals are included in administration costs the estimated financial impact increases by 44% from base case to less than \$10 million in Year 1 increasing to \$10 - \$20 million in Year 6.

Quality Use of Medicines

- 6.57 As for the previous submission, quality use of medicines activities outlined in the resubmission were related to the management of skin reactions associated with cetuximab.

Financial Management – Risk Sharing Arrangements

- 6.58 The resubmission proposed a special pricing arrangement consisting of a rebate of [REDACTED]% based on the published ex-manufacturer price. This was increased from the [REDACTED]% rebate proposed in the previous submission. Moreover, the sponsor proposed a risk-sharing arrangement with a [REDACTED]% rebate above a subsidisation cap of [REDACTED] infusions per RM SCCHN patient. This was a lower cap than the [REDACTED] weeks of treatment (or [REDACTED] doses) proposed in the March 2016 submission. It was unclear how a dose-based subsidisation cap will be applied in practice. A further increase in the rebate was proposed in the pre-PBAC response.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended listing of cetuximab for the treatment of patients with previously untreated recurrent and/or metastatic squamous cell carcinoma of the head and neck, on the basis that it should be available only under special arrangements under section 100. The PBAC is satisfied that there is a clinical need in this patient population and that, for some patients, cetuximab provides a modest

improvement in overall survival, progression free survival and response rates over chemotherapy alone. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost effectiveness of cetuximab could be brought into an acceptable range with a reduced effective price.

- 7.2 The resubmission proposed that cetuximab will be administered with platinum based CT in patients in whom systemic therapy for RM SCCHN is appropriate. The PBAC has previously acknowledged that there is a clinical need for treatments for patients with RM SCCHN. The PBAC also noted the input from consumer comments and the sponsor hearing regarding the clinical need for treatment in this patient population.
- 7.3 The PBAC noted that the EXTREME trial enrolled patients with the equivalent of a performance status 0-2 and considered that for the PBS listing inclusion of the clinical criteria for patients to have ECOG performance status of 0-2 would be appropriate. The PBAC noted that the requested condition (SCCHN) is not a defined term in the SNOWMED Clinical Terminology Australian Release, but the Committee considered that the requested indication in this resubmission should be modified to read; recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx. This is consistent with the trial population and with other requests for listing in these conditions. The PBAC also advised that the clinical criterion that the condition must be previously untreated should remain in the restriction.
- 7.4 The PBAC previously accepted platinum-based chemotherapy alone as the appropriate comparator for RM SCCHN in the oral cavity subgroup and the Committee agreed with ESC that this is also the appropriate comparator for the broader RM SCCHN population.
- 7.5 The PBAC had previously accepted a claim of superior comparative effectiveness for cetuximab + CT with respect to OS, PFS and response rates based on the EXTREME trial, however the magnitude of the benefits (2.7 months gain in OS and 2.3 months gain in PFS in the ITT population) was small.
- 7.6 The ESC advised that although the resubmission appropriately presented evidence for the ITT population and a meta-analysis with other anti-EGFR antibodies, there was no compelling evidence in the resubmission to change PBAC's previous conclusions about the clinical claim. The PBAC noted that the pooled results indicated a smaller incremental benefit compared to the results of the EXTREME trial. The PBAC considered that the EXTREME trial may present the most favourable results for the EGFR + CT combination in patients with RM SCCHN.
- 7.7 The PBAC reiterated its view from the March 2016 meeting that the addition of cetuximab to platinum-based chemotherapy is inferior to platinum-based chemotherapy alone in terms of comparative safety.
- 7.8 The PBAC considered that the base case ICER presented in the resubmission was underestimated due to the factors identified in the commentary and as noted by the

ESC. The PBAC considered a base case incorporating the following to be appropriate (i) costs calculated using the accrued cost method, assuming that for subsequent cetuximab infusions, █% of patients receive 1 x 500 mg vial and the remaining █% receive 4 x 100 mg vials; (ii) differential utilities (trial-based utility values as per resubmission); (iii) a 5 year time horizon; (iv) █% fortnightly dosing; (v) applying a ratio of █/24.3 (█) to account for not all patients receiving treatment up until the time of progression; and (vi) extrapolation using the Weibull function. The PBAC noted the ICER for this scenario was \$75,000 - \$105,000 using the \$█/100 mg price proposed in the pre-PBAC response.

- 7.9 The PBAC considered this base case may still overestimate the incremental benefit because the model used PFS and OS from the EXTREME trial which the Committee considered may overestimate the benefit associated with EGFR + CT, and incorporated treatment specific (differential) utilities for the progression health state which were poorly supported.
- 7.10 The PBAC advised that cetuximab would be cost-effective at a price that results in an ICER for the revised base case that is \$45,000 - \$75,000 per QALY (<\$█/100 mg vial).
- 7.11 The PBAC noted the financial estimates may be underestimated based on the dosing, uptake and administration cost assumptions. However, the PBAC considered it appropriate for the financial estimates to be based on use as presented in the submission with the reduced price required for cetuximab to be cost-effective. The PBAC noted the financial impact associated with the listing of cetuximab would be reduced compared with the estimates presented in the resubmission as a result of the price reduction required for cetuximab to be considered cost-effective.
- 7.12 The PBAC did not recommend that cetuximab should be treated as interchangeable on an individual patient basis with any other drug.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review as the Committee has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
CETUXIMAB Injection, 100 mg/20 mL Injection, 500 mg/100 mL	880 mg	0	Erbitux	Merck Serono Aust

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Category/Program:	Section 100 (Efficient Funding of Chemotherapy (EFC – Private Hospital) Section 100 (Efficient Funding of Chemotherapy (EFC – Public hospital)
PBS indication:	Stage III, IVa or IVb squamous cell cancer of the oral cavity, pharynx or larynx
Treatment phase:	Initial treatment
Restriction:	<input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be recurrent or metastatic SCCHN AND The condition must be previously untreated AND Patient must have a WHO performance status of 0 to 2 AND The treatment must be commenced in combination with platinum-based chemotherapy

Name, Restriction, Manner of administration and form	Max Amt	No. of Rpts	Proprietary Name and Manufacturer	
CETUXIMAB Injection, 100 mg/20 mL Injection, 500 mg/100 mL	550 mg	22	Erbix	Merck Serono Aust

Category/Program:	Section 100 (Efficient Funding of Chemotherapy (EFC – Private Hospital) Section 100 (Efficient Funding of Chemotherapy (EFC – Public hospital)
PBS indication:	Stage III, IVa or IVb squamous cell cancer of the oral cavity, pharynx or larynx
Treatment phase:	Continuing treatment
Restriction:	<input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have progressive disease

9 Context for decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Patients with RM SCCHN have a high and currently unmet need for effective treatments. Merck is therefore delighted that cetuximab has received a positive recommendation for this indication and looks forward to working with the Department to secure the listing as soon as possible.