

6.4 CETUXIMAB
solution for intravenous (IV) infusion;
100 mg in 20 mL & 500 mg in 100 mL;
Erbitux[®]; Merck Serono Pty Ltd.

1 Purpose of Application

1.1 To request Section 100 Authority Required listing of cetuximab as a first-line treatment in combination with chemotherapy for patients with metastatic colorectal cancer (mCRC) whose tumours have RAS wild-type (WT) status.

2 Requested listing

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

Category / Program	Section 100 (Efficient Funding of Chemotherapy (EFC – Private Hospital) Section 100 (Efficient Funding of Chemotherapy (EFC – Public hospital))
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	---
Severity:	Metastatic
Condition:	colorectal cancer
PBS indication:	Metastatic colorectal cancer
Treatment phase:	Initial treatment
Restriction level / method:	<input type="checkbox"/> Restricted benefit <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 (PUBLIC HOSPITAL ONLY)

Public Summary Document – November 2014 PBAC Meeting

Clinical criteria:	<p>Patient must have RAS wild-type metastatic colorectal cancer</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less</p> <p>AND</p> <p>The condition must be previously untreated</p> <p>AND</p> <p>The treatment must be in combination with first-line chemotherapy.</p>
Administrative advice	Special Pricing Arrangements apply.

Name, Restriction, Manner of administration form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
CETUXIMAB Injection, 100 mg/20mL Injection, 500 mg/ 100 mL	550 mg	18	Erbix	SG

Category / Program	Section 100 (Efficient Funding of Chemotherapy (EFC – Private Hospital)) Section 100 (Efficient Funding of Chemotherapy (EFC – Public hospital))
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	---
Severity:	Metastatic
Condition:	Colorectal cancer
Treatment phase:	Continuing treatment
Restriction:	Section 100 (Efficient Funding of Chemotherapy (EFC)) Private Hospital/Private Clinic Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	<p>Patient must have RAS wild-type metastatic colorectal cancer</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>Patient must not have progressive disease</p> <p>AND</p> <p>The treatment must be in combination with first-line chemotherapy.</p>
Administrative advice	Special Pricing Arrangements apply.

- 2.1 The basis for the requested listing is a cost-minimisation analysis of cetuximab + FOLFIRI compared with bevacizumab + FOLFIRI in the proposed population.

- 2.2 The key difference between this resubmission and previous submissions is that cetuximab has been requested for mCRC patients whose tumours have RAS WT status rather than KRAS WT status. This is consistent with recent changes in approvals by the TGA and the European Medicines Agency (EMA). The ESC noted that the resubmission also requested to amend KRAS WT to RAS WT status in the current second-line PBS restriction of cetuximab for the treatment of mCRC. The PBAC recalled that it had already recommended this change to the current second-line restriction of cetuximab at its July 2014 meeting as a flow-on change from its consideration of panitumumab.
- 2.3 The proposed restriction specifies that patients should have a WHO performance status of 0 to 2. The proportion of patients enrolled in the FIRE-3 trial with a performance status of 2 was low (11/259 (2%)). In addition, the ESC noted that that continuing treatment does specify the WHO performance status. The Product Information (PI) for cetuximab recommends that special attention should be given to the use of cetuximab in patients with reduced performance status. The ESC noted that PSCR (p1) states that the sponsor is willing to limit cetuximab to patients with WHO 0 or 1.
- 2.4 The PBAC considered that the amendment of the restriction to patients with WHO performance status of 1 or less is appropriate.

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

3 Background

- 3.1 Cetuximab is currently TGA registered for the treatment of RAS WT mCRC, including as first-line treatment in combination with FOLFOX, and 5-fluorouracil/folinic acid plus irinotecan.
- 3.2 This is the third submission to the PBAC for cetuximab to be considered as a first-line treatment for mCRC.
- 3.3 In March 2010, the PBAC rejected a submission for first-line cetuximab treatment of KRAS WT mCRC on the basis that bevacizumab was not the appropriate comparator (the suggested comparator was chemotherapy alone). It was unlikely that cetuximab would substitute for bevacizumab because at the time the K-RAS status of most mCRC patients was unknown when treatment commenced. The submission was also rejected on the basis of uncertainty regarding the indirect comparison.
- 3.4 In November 2013, the second submission of cetuximab for first-line treatment of KRAS WT mCRC was withdrawn. The PBAC noted with concern the emerging data regarding a reduced treatment effect associated with the use of cetuximab (and panitumumab) on tumours with a broader range of RAS mutations than the exon 2 mutations detected with KRAS testing.

4 Clinical place for the proposed therapy

- 4.1 Bowel cancer is the second most common cancer in Australia with 15,840 cases in 2012. In 2010, it was the second leading cause of cancer death in Australia, with 3,982 deaths. The average life expectancy of a patient with mCRC is less than 3 years.
- 4.2 Current treatment options for first-line treatment of mCRC are chemotherapy alone (e.g. FOLFIRI or FOLFOX) or chemotherapy plus bevacizumab. Bevacizumab is not PBS-subsidised for later-line treatment.
- 4.3 The PBAC noted that the clinical need for first-line cetuximab therapy is low because both bevacizumab and anti-EGFR antibodies (cetuximab and panitumumab) are already PBS subsidised. The current PBS restrictions are that bevacizumab needs to be used first line (i.e. before an anti-EGFR antibody), and the anti-EGFR antibody needs to be used in later-line treatment.

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

5 Comparator

- 5.1 The resubmission nominates bevacizumab as the only comparator. Chemotherapy alone is also an additional comparator as eligibility for monoclonal antibodies on the PBS also requires suitability for chemotherapy.

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 presented clinical case studies and discussed the natural history of the disease and how the drug would be used in practice. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2), organisations (5) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with cetuximab including the survival benefit of the drug, improved access afforded by PBS listing and fewer side effects.
- 6.3 The PBAC noted the advice received from Bowel Cancer Australia clarifying the likely use of cetuximab in clinical practice. The PBAC specifically noted the advice that the use of cetuximab shows a survival benefit over bevacizumab. The PBAC noted that this advice was not adequately supported by the evidence provided in the submission.

Clinical trials

- 6.4 The resubmission was based on one head-to-head randomised trial (FIRE-3) comparing cetuximab with bevacizumab, in combination with FOLFIRI, for first-line treatment of mCRC. Thus the same FIRE-3 trial (cetuximab + FOLFIRI vs bevacizumab + FOLFIRI), presented in the previous submission for an ITT population with KRAS WT tumours, was reproduced in the current resubmission with updated results for a newly proposed subgroup of mCRC patients with RAS WT tumours (n=407 for the RAS evaluable population and n=342 for RAS WT). The subgroup analysis was retrospective for the RAS WT biomarker subgroup, as there were concerns regarding inadequate targeting using KRAS WT status alone. The ESC noted that preliminary results from a RAS WT subgroup analysis of the CALGB/SWOG 80405 trial were recently presented at the European Society for Medical Oncology (ESMO) 2014 Congress and requested that details of these results should be included in the ESC Advice and its meta-analyses where possible.
- 6.5 Details of the FIRE-3 and CALGB/SWOG 80405 trials are provided in the table below.

Key trials to support the request to list cetuximab as a first-line treatment for RAS WT mCRC

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
FIRE-3	National Institutes of Health Clinical Trial Registry Heinemann V. 5-FU, folinic acid and irinotecan (FOLFIRI) plus cetuximab versus FOLFIRI plus bevacizumab in first-line treatment colorectal cancer (CRC). NCT00433927.	October 2012
	Protocol AIO CRC 0306 Randomized study to investigate the efficacy of FOLFIRI in combination with cetuximab vs. bevacizumab in the first-line treatment of metastatic colorectal cancer. Clinical data cut-off date: 17 April 2013	Updated February 2014
	Publications Heinemann V, von Weikersthal F, Decker T, <i>et al.</i> Randomised comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3).	2013 ASCO Annual Meeting
	Stintzing S, Jung A, Neumann J, <i>et al.</i> FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patient with metastatic colorectal cancer (mCRC): analysis of patients with KRAS-mutated tumours in the randomized German AIO study KRK-0306.	<i>Journal of Clinical Oncology</i> , 2011; 29 (Suppl 1) Abstract 3575
	Heinemann V, von Weikersthal F, <i>et al.</i> Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wild-type metastatic colorectal cancer: The FIRE-3 trial (AIO KRK 0307).	<i>Onkologie</i> 2013, 36 (suppl 7):104 Abstract No: V388
	Modest D, <i>et al.</i> FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3).	<i>Annals of Oncology</i> , 2013; 24 (Suppl 4):iv11-24.
Stintzing S <i>et al.</i> Mutations within the EGFR signaling pathway: Influence	<i>Journal of Clinical</i>	

	<p>on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients.</p> <p>Stintzing S <i>et al.</i> Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: A randomized phase III study of FOLFIRI plus cetuximab (cet) or bevacizumab (bev) as first-line treatment (tx) for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients.</p> <p>Stintzing S, von Weikersthal F, Decker, <i>et al.</i> FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patient with metastatic colorectal cancer - subgroup analysis of patients with KRAS: mutated tumours in the randomised German AIO study KRK-0306. Letter to the editor.</p> <p>Pietrantonio F, Garassino MC, Torri V, <i>et al.</i> Reply to FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS-mutated tumours in the randomised German AIO study KRK-0306.</p>	<p><i>Oncology</i>, 2014; 32 (suppl 3):abstr 445.</p> <p><i>European Journal of Cancer</i>, 2013; 49(Suppl 3):s8-9 Abs LBA 17</p> <p><i>Annals of Oncology</i>, 2012; 23 (7): 1693-9.</p> <p><i>Annals of Oncology</i>, 2012; 23 (10): 2771-2772</p>
CALGB/SWOG 80405	<p>Publications</p> <p>Venook AP, Blanke CD, Niedzwiecki D, Lenz HJ, <i>et al.</i> Cancer and Leukemia Group B/Southwest Oncology Group trial 80405: a phase III trial of chemotherapy and biologics for patients with untreated advanced colorectal adenocarcinoma.</p> <p>Venook AP, Blanke CD, Niedzwiecki D, Lenz HJ, <i>et al.</i> Revisiting the Cancer and Leukemia Group B/Southwest Oncology Group 80405 Trial: A Phase III Trial of Chemotherapy and Biologic Agents for Patients with Untreated Advanced Colorectal Adenocarcinoma.</p> <p>Abstract</p> <p>Lenz H, Innocenti F, Blanke C, <i>et al.</i> Abstract 5010 - CALGB/SWOG 80405: PHASE III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded ras analyses untreated metastatic adenocarcinoma of the colon or rectum (MCRC)</p>	<p><i>Clin Colorectal Cancer</i>, 2005, 5(4): 292-294</p> <p><i>Clin Colorectal Cancer</i>, 2007, 7(1): 536-538</p> <p>European Society of Medical Oncology (ESMO) 2014.</p>

Source: FIRE-3: Table B.2-2, p44 of the resubmission and Appendix 8 to the resubmission; CALGB/SWOG 80405: <http://www.esmo.org/Conferences/ESMO-2014-Congress> and <https://clinicaltrials.gov/>

6.6 The key features of the FIRE-3 and CALGB/SWOG trials are summarised in table below.

Key features of the FIRE-3 and CALGB/SWOG 80405 trials

Trial	N	Design/approx. duration of follow-up	Risk of bias/confounding	Patient population	Outcome(s)
Direct comparison: cetuximab + FOLFIRI vs bevacizumab + FOLFIRI					
FIRE-3 • ITT: KRAS WT	592	MC, R, OL 33 mths cmab, 39 mths bmab	ORR and PFS: moderate risk of bias*. OS: high risk of confounding**. Estimation of adverse events: high risk of bias due to lack of concealment of allocation	First-line KRAS WT mCRC	Primary: ORR Secondary: PFS, OS

<ul style="list-style-type: none"> Post hoc subgroup analysis: RAS WT 	342	No RAS WT data	ORR and PFS: moderate risk of bias*. OS: high risk of confounding**. Estimation of adverse events: high risk of bias due to lack of concealment of allocation Benefits of randomisation not retained in subgroup analysis	First-line RAS WT mCRC	Primary: ORR Secondary: PFS, OS
<p><u>CALGB/SWOG 80405^β</u></p> <ul style="list-style-type: none"> ITT: KRAS WT Post hoc subgroup analysis: RAS WT 	1,137 562	MC, R, OL Treatment duration not reported Retrospective subgroup analysis.	Cannot be assessed as only an abstract is available.	First-line KRAS WT mCRC First-line RAS WT mCRC	Primary: OS Secondary: PFS, ORR

MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; cmab = cetuximab; bmab = bevacizumab; ORR = overall response rate; K/RAS WT = K/rat sarcoma viral oncogene wild-type

* Measurement of tumour response and progression by investigators are subject to bias given the subjectivity of measuring tumour response. A blinded centralised review is likely to mitigate concerns relating to non-blinded assessment (although this would not necessarily address systematic differences between trial arms in the frequency of assessment)².

** Subsequent treatments post-progression are likely to be determined by investigators. The allocation of second-line treatments is not randomised and likely to be dependent on prognostic factors at time of progression. Differences in prognostic factors and subsequent post-progression treatment effects could confound overall survival results.

^β CALGB/SWOG 80405: 2,334 KRAS wild type patients were randomised. The final number included 1,137 patients (bevacizumab arm: N=559, 324 (58%) evaluable for extended RAS analysis; cetuximab arm: N=578, 346 (60%) evaluable for extended RAS analysis). The ESMO 2014 RAS wild type subgroup analysis of overall survival was based on 526 patients (256 in the bevacizumab arm and 270 in the cetuximab arm).

Source: compiled during the evaluation

6.7 Three other cetuximab trials in the first-line setting (for which RAS WT data are available) were relevant to support a comparison of cetuximab plus chemotherapy with chemotherapy alone. Two of the trials used chemotherapy regimens that were oxaliplatin-based and one was irinotecan-based:

- OPUS compared cetuximab + FOLFOX versus FOLFOX alone;
- COIN compared oxaliplatin plus a fluoropyrimidine (capecitabine or 5FU plus leucovorin (LV) as determined by the patient's oncologist) with or without cetuximab; and
- Crystal compared cetuximab + FOLFIRI versus FOLFIRI alone.

Comparative effectiveness

Relative to bevacizumab and chemotherapy

FIRE-3

6.8 The primary endpoint of overall response rate (ORR) and key secondary outcomes of progression-free survival (PFS) and overall survival (OS) for the RAS WT population in the FIRE-3 trial are summarised in the tables below. The Kaplan-Meier curves for OS are also presented in the figure below.

Results of the primary endpoint – overall response rate in RAS WT mCRC patients in FIRE-3

	Cetuximab + FOLFIRI (N=171)	Bevacizumab + FOLFIRI (N=171)	OR [95% CI]**	RD [95% CI]**
ORR*, % (n) [95% CI],	65.5% (112) [57.9%, 72.6%]	59.6% (102) [51.9%, 67.1%]	1.28 [0.83, 1.99]	5.9% [-4.4%, 16.1%]

Values in italics were calculated during the evaluation.

*Investigator assessment of all RAS WT population – primary endpoint

** cetuximab versus bevacizumab

RAS WT = rat sarcoma viral oncogene wild-type; FOLFIRI = 5-fluorouracil, folinic acid and irinotecan; OR = odds ratio; CI = confidence interval; RD = risk difference; ORR = overall response rate (complete response + partial response);

Source: Revised from Table B.6-2, p73 of the resubmission

Results of progression-free survival and overall survival in RAS WT mCRC patients in FIRE-3

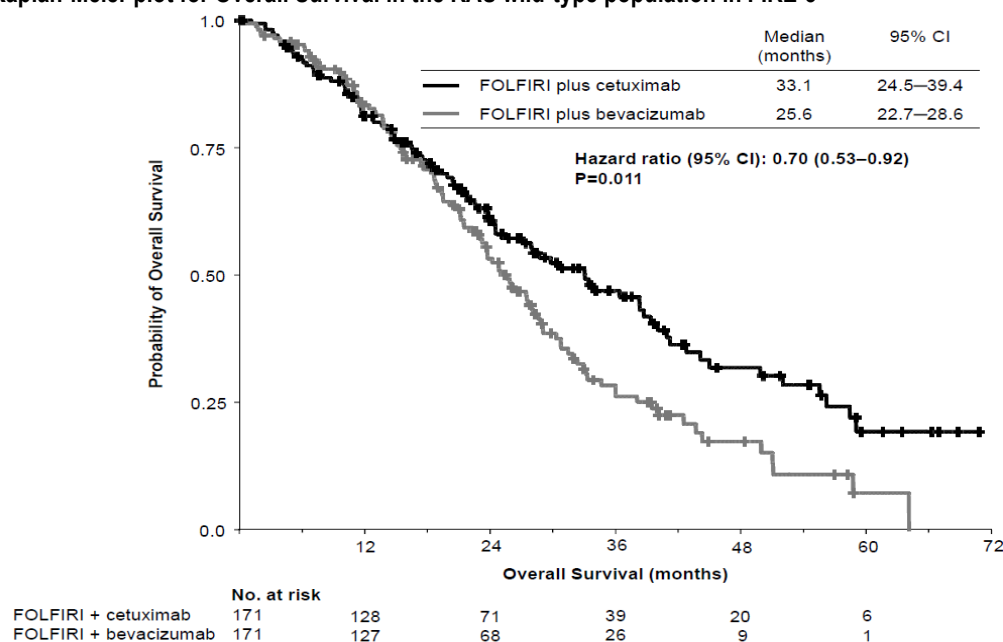
	Cetuximab + FOLFIRI (N=171)	Bevacizumab + FOLFIRI (N=171)	Absolute difference (months)	HR [95% CI]	p-value*
Median PFS, months [95% CI]	10.4 [9.5, 12.2]	10.2 [9.3, 11.5]	+0.2	0.93 [0.74, 1.17]	0.536
Median OS months [95% CI]	33.1 [24.5, 39.4]	25.6 [22.7, 28.6]	+7.5	0.70 [0.53, 0.92]	0.001

*Log-rank test (two-sided) cetuximab versus bevacizumab

RAS WT = rat sarcoma viral oncogene wild-type; FOLFIRI = 5-fluorouracil, folinic acid and irinotecan; HR = hazard ratio; CI = confidence interval; PFS = progression-free survival; OS = overall survival

Source: Table B.6.4, p75 and Table B.6.6, p77 of the resubmission.

Kaplan-Meier plot for Overall Survival in the RAS wild-type population in FIRE-3



Source: data on file.

Dark grey line = cetuximab plus FOLFIRI, light grey line = bevacizumab plus FOLFIRI.

Source: Figure B.6-5, p77 of the resubmission

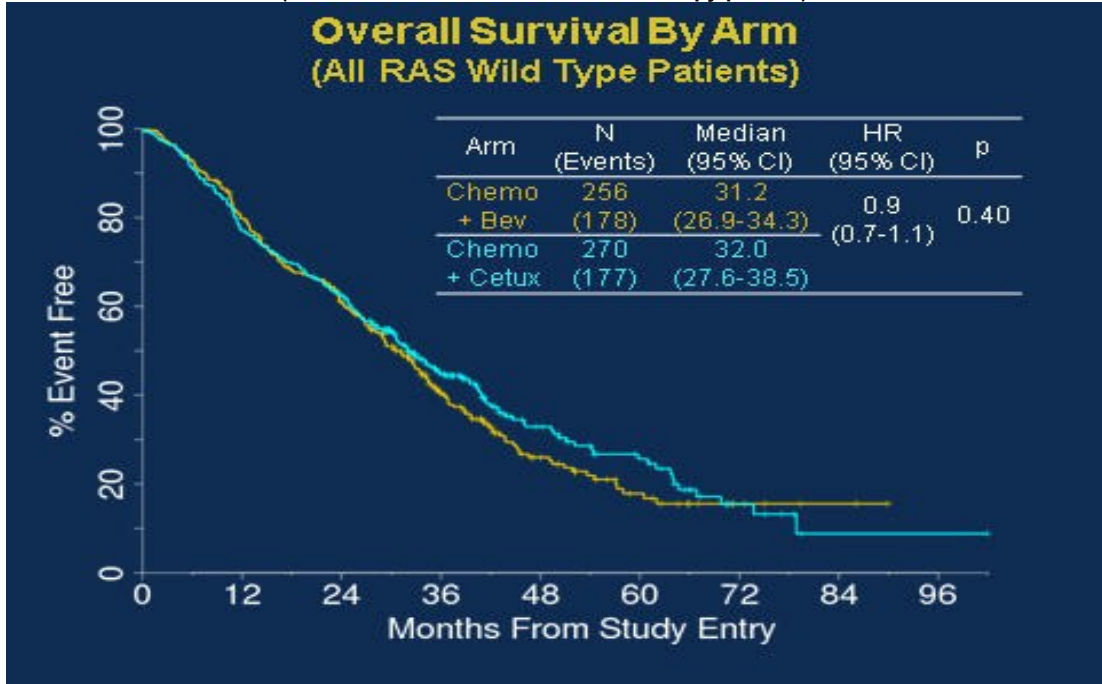
- 6.9 There was no statistically significant difference in the primary endpoint of ORR or the secondary endpoint of PFS between cetuximab and bevacizumab arms for the RAS WT subgroup of the FIRE-3 trial.
- 6.10 The median OS gain observed from the cetuximab arm compared with the bevacizumab arm was 7.5 months corresponding to a statistically significant 30% reduction of mortality favouring patients randomised initially to cetuximab + FOLFIRI. The OS results should be interpreted cautiously for the following reasons.
- The survival curves start separating at around 20 months. This is well beyond the observed median PFS associated with cetuximab treatment (around 10 months) and occurs after the initiation of second-line treatment. Notably, median PFS was not significantly different between the two treatment arms. Overall survival differences appear to be affected by the choice of second-line treatment.
 - Second-line treatments received by patients randomised to cetuximab are not representative of Australian clinical practice. This is because 44% of patients randomised to cetuximab who received second-line treatment upon progression were given bevacizumab, but bevacizumab is not PBS-listed as a second-line therapy for patients with mCRC in Australia. This appears to overestimate the OS gain in patients randomised to first-line cetuximab when compared with Australian clinical practice.

The sponsor has appropriately not relied on these OS results for the non-inferiority claim.

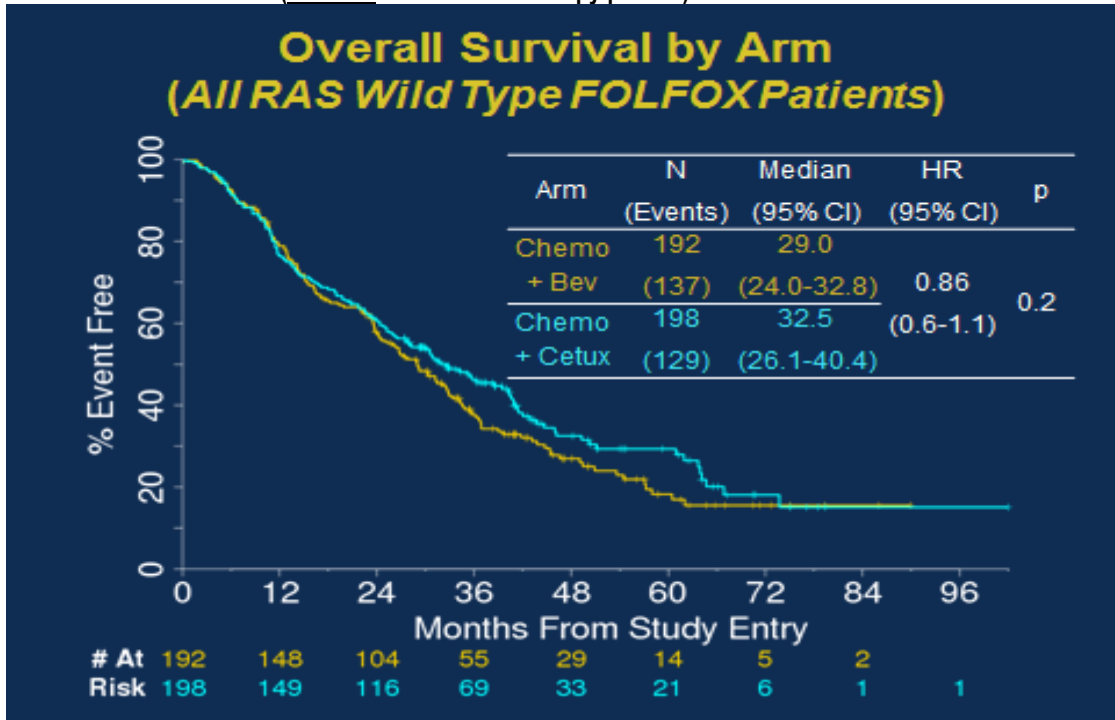
CALGB/SWOG 80405 (all RAS wild type (WT) subgroup analysis)

- 6.11 The CALGB/SWOG 80405 subgroup analysis was post hoc and has yet to be published in the peer-reviewed literature. The Kaplan-Meier plots for the primary endpoint of OS are summarised in the figures below; there was no statistically significant difference between the cetuximab and bevacizumab arms.

Kaplan-Meier plot for the primary endpoint of overall survival in the RAS wild-type subgroup of the CALGB/SWOG 80405 trial (FOLFOX or FOLFIRI as the chemotherapy partner)

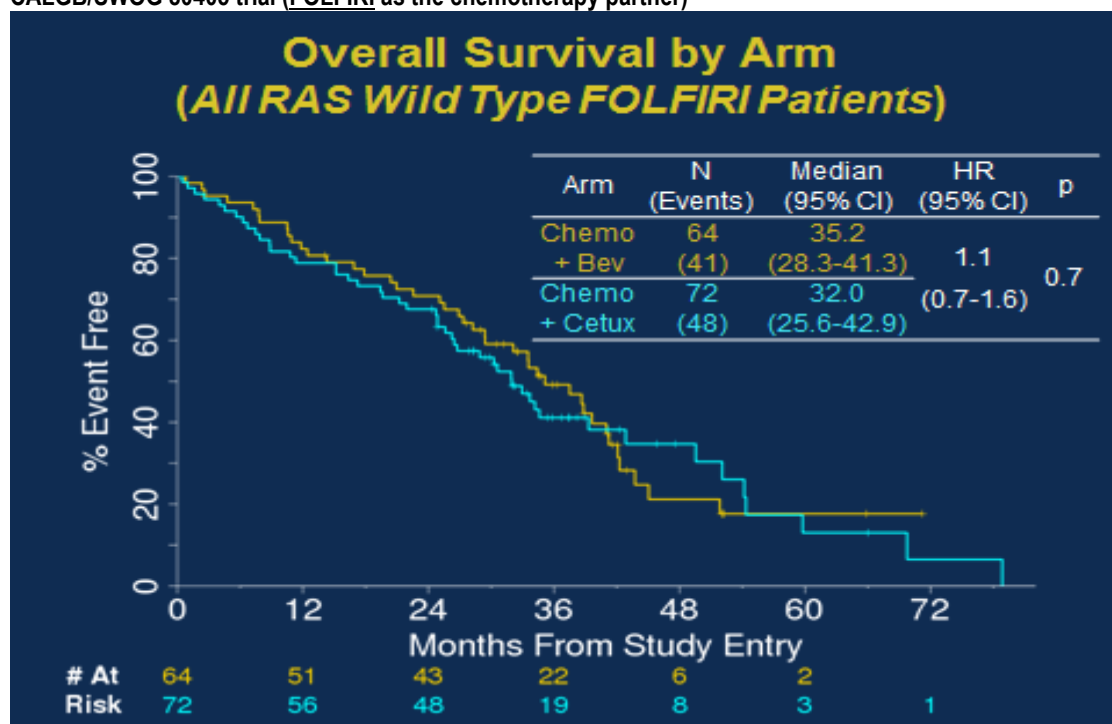


Kaplan-Meier plot for the primary endpoint of overall survival in the RAS wild-type subgroup of the CALGB/SWOG 80405 trial (FOLFOX as the chemotherapy partner)



Source: ESMO 2014 Congress: Abstract 5010, Lenz J et al - CALGB/SWOG 80405

Kaplan-Meier plot for the primary endpoint of overall survival in the RAS wild-type subgroup of the CALGB/SWOG 80405 trial (FOLFIRI as the chemotherapy partner)



Source: ESMO 2014 Congress: Abstract 5010, Lenz J et al - CALGB/SWOG 80405

- 6.12 In the RAS WT subgroup analysis of CALGB/SWOG 80405, there was a numerical difference in the median overall survival of patients receiving bevacizumab that appears to depend on whether it was used with FOLFOX (29.0 months) or FOLFIRI (35.2 months). The difference of approximately six months could be due to imbalances in prognostic factors between the two chemotherapy groups. On the other hand, there was little numerical difference in median overall survival when cetuximab was used with FOLFOX (32.5 months) or FOLFIRI (32.0 months).

Relative to chemotherapy alone

- 6.13 RAS WT analyses are available for three trials which compared cetuximab + chemotherapy versus chemotherapy alone in the first-line setting: CRYSTAL, OPUS and COIN. The tables below summarise the PFS and OS results, respectively. The OS results of these trials, even if affected by patient cross-over between trial arms, are applicable to the Australian PBS setting because cetuximab is available as a post-progression treatment.

First-line cetuximab+chemotherapy versus chemotherapy alone: Progression-free survival (PFS) results in the RAS WT subgroup (KRAS and NRAS Exons 2/3/4)

Irinotecan-based chemotherapy backbone		
CRYSTAL	Cetuximab+FOLFIRI	FOLFIRI alone
N	178	189
Median PFS, months (95% CI)	11.4	8.4
Difference in PFS	+3.0	
HR (95% CI)	0.56 (0.41, 0.76)	



Oxaliplatin-based chemotherapy backbone		
OPUS	Cetuximab+FOLFOX	FOLFOX alone
N	38	49
Median PFS, months (95% CI)	12.0 (NR)	5.8 (4.7, 7.9)
Difference in PFS	+6.2	
HR (95% CI)	0.53 (0.27, 1.04) ^a	
COIN^b	Cetuximab+oxaliplatin and capecitabine (67%) or+FOLFOX (33%)	Oxaliplatin and capecitabine (65%) or FOLFOX (35%)
N	292	289
Median PFS, months (95% CI)	NR PFS data not provided in Maughan et al (2011) ⁴	
Difference in PFS	No difference in PFS	
HR (95% CI)	Maughan et al note (2011) that there was no evidence of PFS benefit seen in any of the genetically defined (RAS and RAF) subgroups.	

^aThe HR of 0.53 was sourced from Appendix 5 (OPUS RAS analysis) to the cetuximab resubmission. This differs from the OPUS 2014 abstract publication by Tejpar et al (20124)³ which indicates the same median PFS estimates but a different HR of 0.43 (95% CI: 0.21, 0.88). The number of patients also differ in the Tejpar report (Cetuximab: N=36; Bevacizumab: N=46). Data cut-off dates are not specified making it difficult to judge the results.

^bKRAS/NRAS Exons 2/3 and BRAF WT.

Sources: Table constructed during the evaluation based on European assessment reports for cetuximab, RAS analyses study publications and Appendices to the resubmission.

First-line cetuximab+chemotherapy versus chemotherapy alone: Overall survival (OS) results in the RAS WT subgroup (KRAS and NRAS Exons 2/3/4)

Irinotecan-based chemotherapy backbone		
CRYSTAL	Cetuximab+FOLFIRI	FOLFIRI alone
N	178	189
Median OS, months (95% CI)	28.4 	20.2 
Difference in OS	+8.2	
HR (95% CI)	0.69 (0.54, 0.88)	
Oxaliplatin-based chemotherapy backbone		
OPUS	Cetuximab+FOLFOX	FOLFOX alone
N	38	49
Median OS, months (95% CI)	19.8 (16.6, 25.4)	17.8 (13.8, 23.9)
Difference in OS	+2	
HR (95% CI)	0.94 (0.56, 1.56) ^a	
COIN^b	Cetuximab+oxaliplatin and capecitabine (67%) or+FOLFOX (33%)	Oxaliplatin and capecitabine (65%) or FOLFOX (35%)
N	292	289
Median OS, months (95% CI)	19.9 (NR)	20.1 (NR)
Difference in OS	-0.2	
HR (95% CI)	1.02 (0.83, 1.24)	

^a The HR of 0.94 was sourced from Appendix 5 (OPUS RAS analysis) to the cetuximab resubmission. This differs from the OPUS 2014 abstract publication by Tejpar et al (20124)³ which indicates different median OS estimates in the cetuximab (20.7 months) and bevacizumab (17.8 months) arms and a different HR of 0.83 (95% CI: 0.49, 1.41). The number of patients also differ in the Tejpar report (Cetuximab: N=36; Bevacizumab: N=46). Data cut-off dates are not specified making it difficult to judge the results.

^bKRAS/NRAS Exons 2/3 and BRAF WT.

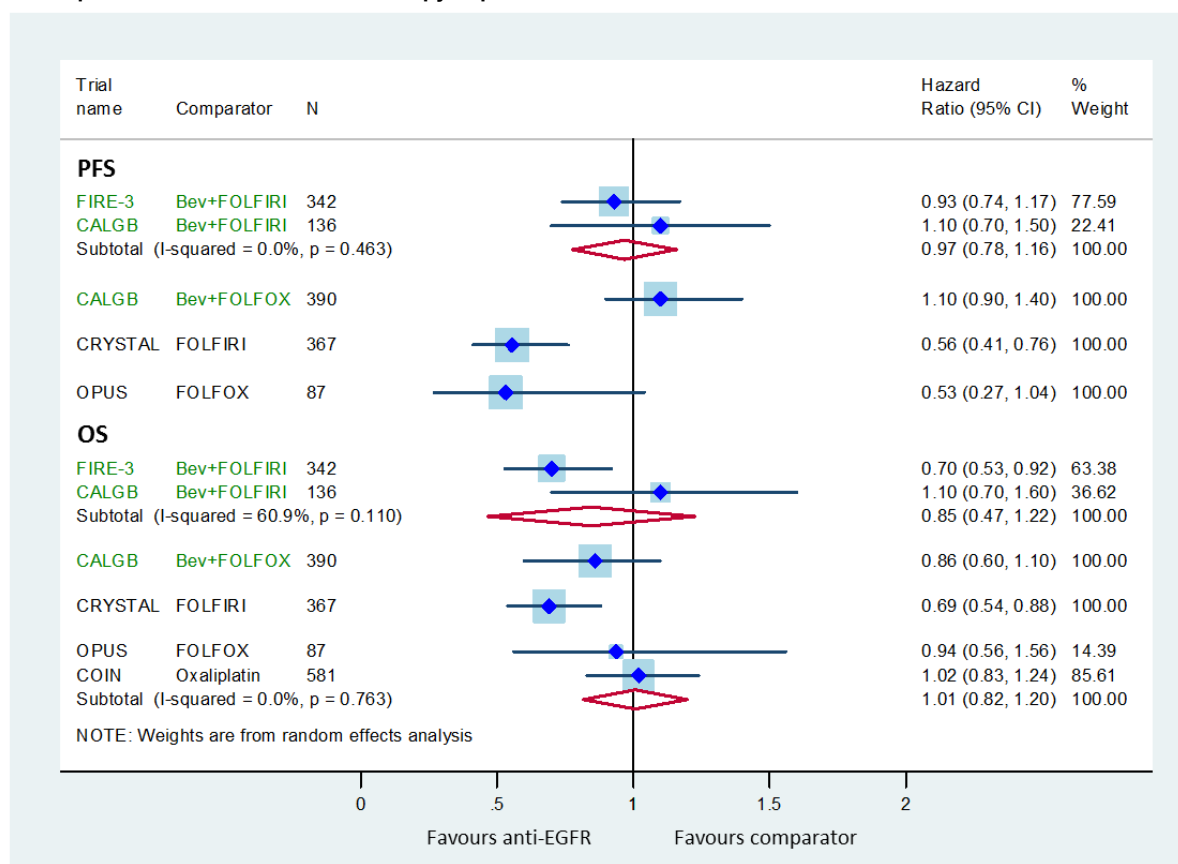
Sources: Table constructed during the evaluation based on European assessment reports for cetuximab, RAS

analyses study publications and Appendices to the resubmission.

Meta-analyses

- 6.14 The meta-analysis of first-line cetuximab trials conducted during the evaluation to compare the addition of cetuximab to chemotherapy with chemotherapy alone or with bevacizumab + chemotherapy (the forest plots below) was extended to include CALGB/SWOG 80405. There was no statistically significant difference in PFS in patients receiving cetuximab or bevacizumab over a background of chemotherapy. OS results were also similar.

Forest plots of first-line cetuximab therapy in patients with RAS WT mCRC



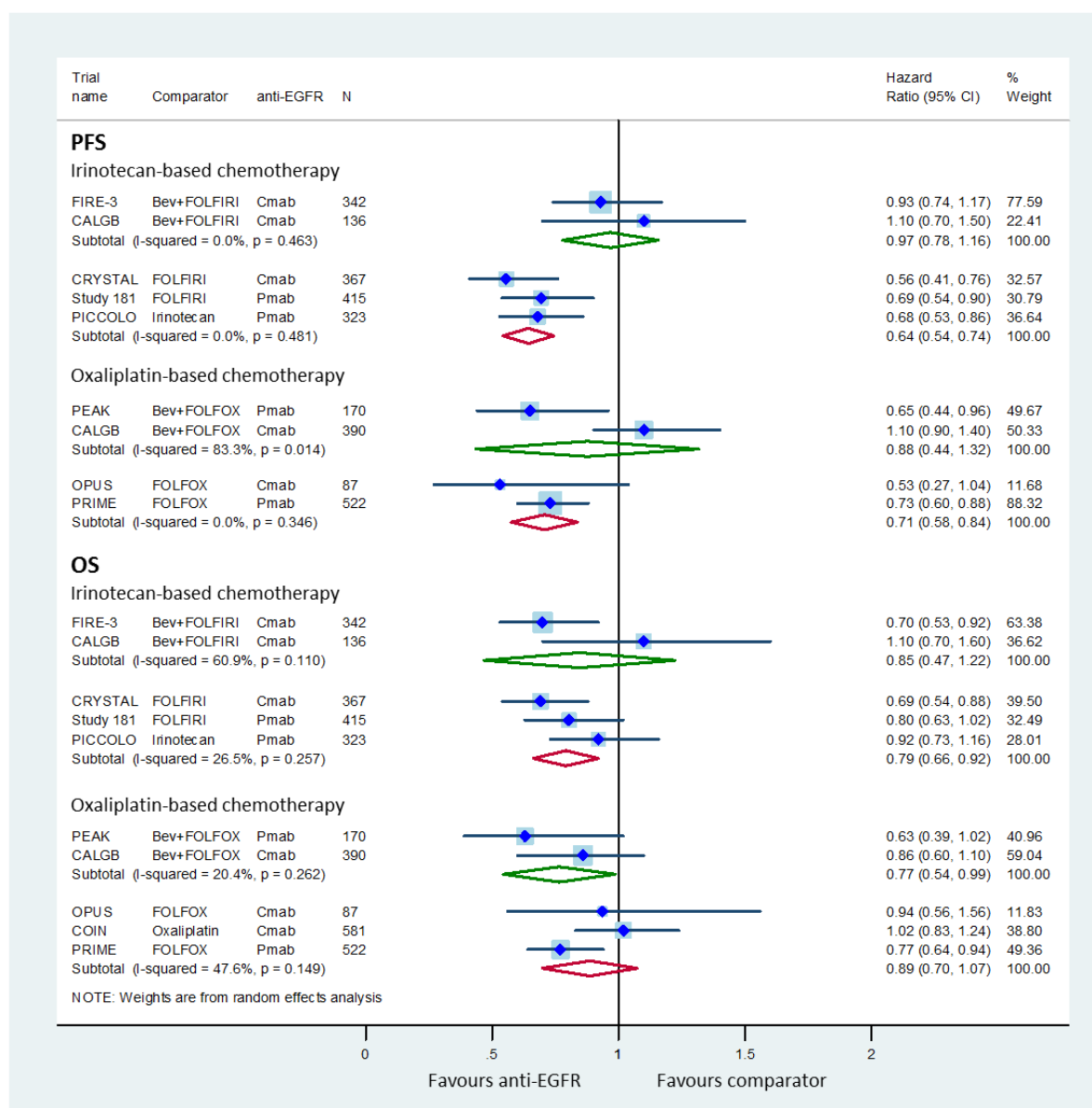
COIN (PFS data for RAS WT not available) = cetuximab + oxaliplatin with capecitabine (66%) or cetuximab + FOLFOX (34%) versus the same chemotherapy regimen FIRE-3 = cetuximab + FOLFIRI vs bevacizumab + FOLFIRI; CRYSTAL = cetuximab + FOLFIRI vs FOLFIRI; OPUS = cetuximab + FOLFOX vs FOLFOX; RAS WT: rat sarcoma viral oncogene homolog wild type; mCRC = metastatic colorectal cancer.

Source: extended in response to ESC request.

- 6.15 The addition of cetuximab to either first-line FOLFOX or FOLFIRI resulted in a superior gain in PFS, but not in OS.
- 6.16 The ESC noted that a similar meta-analysis of all relevant panitumumab and cetuximab trials would be useful in assessing: 1) the comparison of anti-EGFR antibody + chemotherapy versus either chemotherapy alone or versus chemotherapy plus bevacizumab; and 2) whether the extent of incremental benefit of anti-EGFR

antibodies varies with the choice of chemotherapy partner. A meta-analysis of randomised trials comparing the addition of an anti-EGFR antibody to chemotherapy versus an active treatment arm (regardless of line of therapy), in RAS WT mCRC disease, is presented in forest plots below.

Forest plots of anti-EGFR antibody + chemotherapy versus either chemotherapy alone or versus chemotherapy + bevacizumab in patients with RAS wild type mCRC disease. Both first- and later-line trials included.



RAS WT: rat sarcoma viral oncogene homolog wild type; mCRC = metastatic colorectal cancer; Cmab = cetuximab; Pmab = panitumumab; Bev = bevacizumab; FIRE-3 = cetuximab + FOLFIRI vs bevacizumab + FOLFIRI; CRYSTAL = cetuximab + FOLFIRI vs FOLFIRI alone; OPUS = cetuximab + FOLFOX vs FOLFOX alone; COIN = cetuximab + oxaliplatin with capecitabine (66%) or cetuximab + FOLFOX (34%) versus the same chemotherapy regimen alone; PRIME = panitumumab + FOLFOX vs FOLFOX alone; PICCOLO = panitumumab + irinotecan vs irinotecan alone; Study 181 = panitumumab + FOLFIRI vs FOLFIRI alone; CALGB = cetuximab + FOLFIRI or FOLFOX versus bevacizumab + FOLFIRI or FOLFOX – Proportion of FOLFOX or FOLFIRI use, in the all RAS wild type subgroup (46% of the ITT KRAS wild type population), is unknown. In the ITT KRAS wild type

population, the use of FOLFOX was 73%.
Source: prepared in response to ESC request.

- 6.17 PFS: There was a statistically significant gain in median PFS resulting from the addition of an anti-EGFR antibody to chemotherapy (either FOLFIRI or FOLFOX). However, there was no statistically significant difference in PFS resulting from the addition of an anti-EGFR antibody, versus the addition of bevacizumab, to FOLFIRI as a chemotherapy partner. Results for FOLFOX as the chemotherapy partner are associated with significant heterogeneity ($I^2=80%$) and are difficult to interpret.
- 6.18 OS: There was a statistically significant gain in median OS resulting from the addition of an anti-EGFR antibody to an irinotecan-based chemotherapy regimen and a trend favouring the addition of an anti-EGFR antibody to an oxaliplatin-based chemotherapy regimen. The results for addition of an anti-EGFR antibody versus the addition of bevacizumab to FOLFIRI are heterogeneous. The results for FOLFOX suggest a statistically significant difference in OS favouring cetuximab over bevacizumab. All OS results could be potentially confounded by post-progression therapies.

Comparative harms

- 6.19 In relation to the FIRE-3 trial, in the KRAS WT ITT population there were higher frequencies of skin-related adverse events, hepatotoxicity, desquamation, peripheral oedema and laboratory values in the cetuximab + FOLFIRI arm compared to the bevacizumab + FOLFIRI arm. The bevacizumab + FOLFIRI arm was associated with higher frequencies of haemorrhage, nausea, hypertension and nephrotoxicity than the cetuximab + FOLFIRI arm.
- 6.20 There were more Grade ≥ 3 adverse events (AEs) in the cetuximab + FOLFIRI arm compared with the bevacizumab + FOLFIRI arm for the following: skin-related events, hypokalaemia, desquamation and haemotoxicity. Grade ≥ 3 hypertension was fairly similar between treatment arms. The safety data from the FIRE-3 trial are consistent with the different safety profiles of cetuximab and bevacizumab. Skin-related reactions and bleeding events are known to be associated with cetuximab and bevacizumab, respectively.
- 6.21 Grade ≥ 3 AEs in either treatment arm of the RAS WT subgroup of FIRE-3 are summarised in the table below.

Grade ≥3 adverse events occurring in ≥5% of subjects in either treatment arm in the RAS wild-type subgroup in FIRE-3. Only events with ≥5% difference between arms are included.

Adverse Event Category	Cetuximab + FOLFIRI (n=171)	Bevacizumab + FOLFIRI (n=171)
Skin reaction ²	██████████	██████████
Haemotoxicity ¹	██████████	██████████
Acneiform exanthema/rash ^{1,2}	██████████	██████████
Hypokalaemia	██████████	██████████
Desquamation ^{1,2}	██████████	██████████
Nail changes/paronychia ¹	██████████	██████████

¹ Pre-defined AEs from the clinical report form; ² AEs of special interest. If a subject experienced more than one AE within a category, the subject was counted once in that category.

Source: FIRE-3 CSR Table 12-8 p125

- 6.22 In relation to AEs reported in the RAS WT populations from the CRYSTAL and OPUS trials, there were more Grade 3/4 AEs, serious AEs (SAEs), and any AE causing discontinuation of study treatment in the cetuximab + chemotherapy arm compared to the chemotherapy alone arm.

Benefits/harms

- 6.23 A summary of the comparative benefits and harms for cetuximab plus FOLFIRI versus bevacizumab plus FOLFIRI observed in the FIRE-3 trial is presented in the table below.

FIRE-3: Summary of comparative benefits and harms for cetuximab plus FOLFIRI versus bevacizumab plus FOLFIRI in the RAS WT mCRC subgroup

Benefits						
A non-inferiority claim was made on the basis of the primary endpoint, ORR. Overall survival was potentially confounded by post-progression treatments and so has not been reported.						
Outcome	Cmab + FOLFIRI	Bmab + FOLFIRI	RR/HR (95% CI)	Event rate/100 patients		RD (95% CI)
				Cmab + FOLFIRI	Bmab + FOLFIRI	
ORR, n/N	112/171	102/171	RR:1.10 (0.93, 1.29)	No difference		
Median PFS, mths, (95% CI)	10.4 (9.5, 12.2)	10.2 (9.3, 11.5)	HR:0.93 (0.74, 1.17)	No difference		
Harms						
Grade ≥3 AE	Cmab + FOLFIRI n/N	Bmab + FOLFIRI n/N	RR (95% CI)	Event rate/100 patients ^a		RD (95% CI)
				Cmab + FOLFIRI	Bmab + FOLFIRI	
Skin reaction	██████████	██████████	██████████	██████████	██████████	██████████

^aMedian duration of follow-up in FIRE-3 for RAS WT was not provided. KRAS WT: 33 months and 39 months for cetuximab and bevacizumab arms, respectively.

Cmab = Cetuximab; Bmab = Bevacizumab; RD = risk difference; RR = risk ratio, HR = hazard ratio; N = the number of patients in each arm; ORR = overall response rate (complete response plus partial response); PFS = progression-free survival; FOLFIRI = 5-fluorouracil, folinic acid and irinotecan; AE = adverse events

Source: Compiled during the evaluation

- 6.24 On the basis of direct evidence provided by the FIRE-3 trial, for every 100 patients treated with cetuximab + FOLFIRI in comparison to bevacizumab + FOLFIRI:
- there is no difference in overall response rate
 - there is no difference in progression-free survival
 - approximately 26 additional patients would have a Grade ≥ 3 skin reaction up until disease progression
 - approximately 6 additional patients would experience Grade ≥ 3 haemotoxicity
 - approximately 6 additional patients would experience Grade ≥ 3 hypokalaemia.

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

Clinical claim

- 6.25 The resubmission claims that cetuximab is "...at least as good as bevacizumab..." in terms of effectiveness and the two agents have different safety profiles. This claim for comparative effectiveness is supported by the ORR and PFS results from the FIRE-3 trial. The OS results are difficult to interpret due to the uncertain impact of subsequent post-progression treatments. The claim for comparative safety is supported by the FIRE-3 trial safety data.
- 6.26 No claim is made in the resubmission regarding the addition of cetuximab to chemotherapy versus chemotherapy alone as bevacizumab was the only comparator nominated in the resubmission. The trials examining this comparison suggest that for the first-line RAS WT mCRC population, the addition of cetuximab to chemotherapy results in superior comparative effectiveness and inferior comparative safety. The extent of incremental benefit appears to vary with the choice of chemotherapy partner with the use of an oxaliplatin-based regimen being the less compelling chemotherapy partner.
- 6.27 The ESC noted preliminary analysis of the RAS WT subgroup data from the CALGB trial which compared bevacizumab and cetuximab using both oxaliplatin- and irinotecan-based chemotherapies, presented at the 2014 ESMO conference, demonstrated no statistically significant difference in terms of overall survival and progression-free survival, but a statistically significantly higher response in the cetuximab arm (68.6% v 53.6%, $p < 0.01$).
- 6.28 The PBAC considered that the claim of non-inferior comparative effectiveness was supported by its assessment of the overall results of both FIRE-3 and CALGB/SWOG 80405.
- 6.29 The PBAC considered that the claim of non-inferior comparative safety was reasonable noting that cetuximab has a different safety profile compared to bevacizumab.

Economic analysis

- 6.30 The resubmission presents a cost-minimisation analysis based on a non-inferiority claim of cetuximab + FOLFIRI relative to bevacizumab + FOLFIRI as a first-line treatment in RAS WT mCRC patients. However, unlike the previous submission, this resubmission has included the cost of second-line cetuximab in the first-line

bevacizumab arm as a cost-offset without considering any costs of second-line treatments in the first-line cetuximab arm. This is inconsistent. In addition, the clinical claim relates to outcomes up until the point of progression (endpoint of ORR). By including costs past the point of progression, the non-inferiority claim would need to relate to overall survival. To maintain a claim of non-inferiority (while excluding the costs of second-line bevacizumab), overall survival would need to be no worse for patients solely receiving cetuximab + FOLFIRI relative to patients receiving bevacizumab + FOLFIRI plus second-line therapies (including cetuximab). This is not supported by evidence.

- 6.31 The equi-effective doses presented in the resubmission are cetuximab 6,689mg and bevacizumab 3,816mg.
- 6.32 The equi-effective doses presented in the resubmission may be an underestimate given that the average dose intensity reported in the FIRE-3 trial appears to have included patients who have a break in treatment. Furthermore, the dose intensity for the loading dose of cetuximab is incorrect and is an underestimate. This has been revised during the evaluation to the full loading dose (400mg/m²) as used in the previous submission (July 2013).
- 6.33 The median numbers of treatment cycles of cetuximab and bevacizumab observed in FIRE-3 are used in the resubmission to calculate the costs of first-line treatment in the two arms. The mean number of cycles should have been used. This has been corrected during the evaluation.
- 6.34 The re-calculated equi-effective doses are cetuximab 8,356mg and bevacizumab 4,229mg. The ESC noted that the PSCR (p7) presented revised equi-effective doses of cetuximab 8,099mg and bevacizumab 4,134mg. The ESC considered that the evaluator-calculated equi-effective doses of 8,356mg cetuximab vs 4,229mg bevacizumab were more appropriate as it is not clear why the mean duration was rounded to the nearest cycle in the revised PSCR calculation (PSCR p6). The pre-PBAC response did not comment on this advice.
- 6.35 The resubmission has used a 10% PBS sample to establish that 61% of patients who receive first-line chemotherapy will go on to receive second-line therapy. It is unclear whether this estimate is restricted to mCRC patients and whether it is applicable to the proposed listing of cetuximab for first-line therapy. Given that the claim of non-inferiority is based on the FIRE-3 trial, a trial-based estimate would be more appropriate. In the FIRE-3 trial, 25.7% of patients in the bevacizumab arm received second-line cetuximab. Therefore, the proportion of patients receiving second-line EGFR therapy has been sourced from FIRE-3 during the evaluation.
- 6.36 The results of the revised cost-minimisation analysis are summarised in the table below. The listing of first-line cetuximab will cost the Government an additional of [REDACTED] per patient without considering the cost of later-line cetuximab. This reduces to an additional [REDACTED] per patient when later-line cetuximab is a cost offset in the bevacizumab arm. This does not account for any special pricing arrangements currently in place for bevacizumab. The resubmission has proposed that listing first-line cetuximab will result in a cost-saving to Government of [REDACTED] per patient.

Cost-minimisation analysis based on FIRE-3: total cost to the Government

	Cetuximab	Bevacizumab
First-line treatments		
Average drug costs	██████████	██████████
Average infusion costs	██████████	██████████
Average cost to treat adverse events	██████	█
Total cost of first-line treatment	██████████	██████████
Difference (cetuximab – bevacizumab)	██████████	
Cost-offset for second-line cetuximab		
Average drug costs	██████████	
Average infusion costs	██████████	
Average cost to treat adverse events	██████	
Total cost of second-line cetuximab	██████████	
Difference (cetuximab – (bevacizumab + ██████ second-line cetuximab))	██████████	

Source: re-calculated during the evaluation from the cost-minimisation excel spreadsheet provided with the resubmission

6.37 The ESC noted that the cost-minimisation analysis presented in the resubmission and reiterated in the PSCR (p7) adopted the following:

- the costs of second-line cetuximab in the bevacizumab arm were included
- the costs of second-line bevacizumab in the cetuximab arm were excluded
- the proportion of patients receiving later-line cetuximab in the Australian setting ██████ were applied rather than that observed in the FIRE-3 trial (25.7%)
- ██████ of patients were assumed to receive cetuximab on a fortnightly basis.

6.38 The ESC considered those calculations were inappropriate because no evidence had been provided to support non-inferiority in these circumstances. The ESC considered that additional data would be required to support non-inferiority under the assumptions applied in the cost-minimisation analysis. The ESC considered a pragmatic approach that costs treatments up until progression based on available data in FIRE-3 would be more appropriate.

6.39 The PBAC agreed with the ESC that the cost-minimisation analysis should use only costing of first-line treatments and should not include cost offset of avoided second-line cetuximab. The PBAC also agreed with the ESC that the equi-effective doses of 8,356mg cetuximab vs 4,229mg bevacizumab are appropriate.

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

Drug cost/patient/course

6.40 The average drug cost per patient is estimated to be ██████ based on the mean number of cycles of 12.4 (24.8 infusions), an average dose intensity of 71.7% as observed in FIRE-3 and an assumed full loading dose. The weighted cost is based on 25% use in a public hospital setting and 75% use in a community pharmacy setting. This is compared with a drug cost of ██████ per patient for bevacizumab.

Estimated PBS usage & financial implications

6.41 This resubmission was not considered by DUSC.

- 6.42 The resubmission uses an epidemiological approach to determine the eligible population with RAS WT mCRC and then applies a market share approach to determine the proportion of patients receiving first-line treatment with cetuximab. The costs of cetuximab and bevacizumab were re-calculated during the evaluation using the mean number of treatment cycles as observed in FIRE-3 and assuming a full loading dose of cetuximab. The estimated use and financial implications are summarised in the table below.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Number treated* - Nov 2013					
Uptake rate					
Uptake rate Nov 2013					
Infusions					
Infusions - Nov 2013					
Estimated net cost to PBS/MBS					
Net cost to PBS					
Net cost to PBS Nov 2013**					
Net cost to MBS					
Net cost to MBS Nov 2013**					
Net cost PBS/MBS					
Net cost PBS/MBS Nov 2013**					

*The previous submission was for KRAS WT patient population

**revised estimates provided in PSCR for October 2013 ESC meeting.

Source: Compiled during the evaluation

The redacted table shows that the number of patients estimated to receive treatment with cetuximab is less than 10,000 per year. The estimated net cost to the PBS/MBS is less than \$10 million per year.

- 6.43 The resubmission estimates a net cost-saving to the PBS and to the government. This is not reasonable. Revised estimates using mean treatment duration from the FIRE-3 trial and a loading dose intensity of 400mg/m² for cetuximab result in a [redacted] increase in cost to the Government rising to [redacted] by Year 5.
- 6.44 Infusion costs may be underestimated, the proportion of patients receiving second-line cetuximab and the duration of therapy with second-line cetuximab may be overestimated, and no substitution of chemotherapy alone has been considered for patients who would not have received first-line bevacizumab. Consequently, the revised figures may underestimate the cost to Government.
- 6.45 The PBAC noted the submission states that the sponsor has supported a number of quality use of medicines (QUM) initiatives to allow for the identification, management and treatment of the cetuximab-related rash, to ensure consumers and health care professionals use cetuximab safely and effectively, and thus maintain optimal health outcomes for patients for as long as possible.

- 6.46 The PBAC noted cetuximab may be used beyond disease progression therefore, a Risk Share Agreement (RSA) and a note of the restriction stating “Patient must not switch chemotherapy partners whilst maintaining an anti-EGFR antibody backbone in the face of progressive disease” are necessary for managing the risk.
- 6.47 The PBAC noted that the sponsor was willing to enter into a confidential RSA for cetuximab for first-line mCRC treatment, to prevent any increase to the current total cost to Government associated with the first-line treatment of patients with mCRC, which currently includes treatment with bevacizumab only. No change to the existing RSA for cetuximab in later line treatment of mCRC was proposed by the sponsor.
- 6.48 The PBAC considered, among other matters, that its assessment that the cost-effectiveness of cetuximab would be acceptable if the measures below were implemented to contain risks associated with the cost of the drug to the PBS:
- Cetuximab in first-line mCRC join the bevacizumab RSA, and associated costs be contained within the existing Subsidisation Caps, currently in place for this indication ; and
 - If bevacizumab is in turn made available in second-line treatment of mCRC, to allow effective management of the agreement, the current RSA for cetuximab used in second-line should be combined with the RSA for first-line mCRC, with appropriate reduction in the Subsidisation Caps based on the new estimates and price.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of cetuximab for the first-line treatment of metastatic colorectal cancer, on a cost-minimisation basis compared with bevacizumab. The PBAC agreed that it should be available only under special arrangements under Section 100 - Efficient Funding of Chemotherapy (EFC – Public /Private Hospital). The PBAC recalled that the amendment of cetuximab later-line restriction from KRAS WT to RAS WT status was recommended at its July 2014 meeting when recommendation for the equivalent amendment of panitumumab PBS restriction was made.
- 7.2 The PBAC agreed with ESC that the equi-effective doses are 8,356mg cetuximab vs 4,229mg bevacizumab based on the FIRE-3 trial data.
- 7.3 The PBAC considered that the requested restriction should 1) include a note stating “Patient must not switch chemotherapy partners whilst maintaining an anti-EGFR antibody backbone in the face of progressive disease” in order to help prevent cetuximab being used beyond disease progression; 2) amend WHO performance status to be 1 or less; 3) limit use to a course of cetuximab for mCRC once in a life time (and allow a switch to panitumumab during a course only according to the arrangements already in place for PBS subsidy of later-line therapy); 4) indicate anti-EGFR antibody and anti-VEGF antibody cannot be used at the same time.
- 7.4 The PBAC considered that the clinical need for first-line cetuximab therapy is low because both bevacizumab and anti-EGFR antibodies (cetuximab and panitumumab)

are already PBS subsidised. The current PBS restrictions on practice are that bevacizumab needs to be used first-line (i.e. before an anti-EGFR antibody), and that anti-EGFR antibodies need to be used in later-line treatment. Listing of a first-line anti-EGFR antibody (cetuximab) would theoretically increase choice in terms of first-line treatment, but overall would reduce options for patients receiving first-line cetuximab as bevacizumab is not currently PBS listed for second-line treatment and patients would therefore not be eligible for bevacizumab. Therefore, second-line therapy of bevacizumab would need to be available for patients with a RAS wild type status who have failed first-line treatment of cetuximab.

- 7.5 The PBAC noted that, in the FIRE3 trial, 40% of patients in the bevacizumab + FOLFIRI arm (RAS WT subgroup) received an anti-EGFR antibody (panitumumab or cetuximab) as post-progression therapy. This option reflects the current PBS listings of these medicines. However, 44% of patients in the cetuximab + FOLFIRI arm received bevacizumab as post-progression therapy, which is not allowed using the current PBS listing of bevacizumab. The PBAC considered that, as reflected in FIRE3, it is a standard practice to cross over use of an anti-EGFR antibody (cetuximab or panitumumab) and an anti-VEGF antibody (bevacizumab) at disease progression.
- 7.6 As a consequence, the PBAC also signalled its intention to recommend that the restriction for bevacizumab in mCRC also be amended to allow its subsidised use after cetuximab in RAS WT mCRC. In this regard, the foreshadowed restriction would 1) include a note stating “Patient must not switch chemotherapy partners whilst maintaining a bevacizumab backbone in the face of progressive disease” in order to help prevent bevacizumab being used beyond disease progression; 2) retain WHO performance status to be 1 or less; 3) limit use to a course of bevacizumab for mCRC once in a life time; 4) indicate anti-EGFR antibody and anti-VEGF antibody cannot be used at the same time. The PBAC also signalled that it would not support subsidising any increased bevacizumab dose in second-line compared to first-line therapy.
- 7.7 The PBAC agreed that bevacizumab is an appropriate comparator.
- 7.8 The PBAC agreed that cetuximab with FOLFIRI or FOLFOX is non-inferior in effectiveness in first-line treatment of metastatic colorectal cancer compared with bevacizumab with FOLFIRI or FOLFOX, noting also that cetuximab and bevacizumab have different safety profiles.
- 7.9 The PBAC agreed with the ESC that the cost-minimisation analysis should use only costing of first-line treatments and should not include cost-offsets of avoided second-line cetuximab because both cetuximab and bevacizumab were crossed over at disease progression in both arms of the FIRE 3 trial.
- 7.10 The PBAC agreed with the ESC that the cost to Government may be underestimated due to the underestimate of infusion costs and overestimate of the proportion of patients receiving second-line cetuximab and the duration of therapy with second-line cetuximab.
- 7.11 The PBAC recommended that cetuximab should not be treated as interchangeable with any other drugs.

- 7.12 The PBAC advised that cetuximab is not suitable for prescribing by nurse practitioners.
- 7.13 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:

Recommended

8 Recommended listing

8.1 Create new first-line cetuximab metastatic CRC listings as follows:

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

Category / Program	Section 100 (Efficient Funding of Chemotherapy (EFC)) for Public/Private Hospital Use
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Metastatic
Condition:	Colorectal cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <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 OR <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have RAS wild-type metastatic colorectal cancer, AND Patient must have a WHO performance status of 1 or less, AND The condition must be previously untreated, AND The treatment must be in combination with first-line chemotherapy, AND

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	The treatment must be the sole PBS-subsidised anti-EGFR antibody therapy for this condition.
Administrative advice	<p>Note Special Pricing Arrangements apply.</p> <p>Note Cetuximab is not PBS-subsidised for use in combination with another anti-EGFR antibody or in combination with an anti-VEGF antibody.</p>

Name, Restriction, Manner of administration and form	Max. Qty	Nº.of Rpts	Proprietary Manufacturer	Name and
CETUXIMAB Injection, 100 mg/20 mL Injection, 500 mg/100 mL	550 mg	18	Erbitux	SG

Category / Program	Section 100 (Efficient Funding of Chemotherapy (EFC)) for Public/Private Hospital Use
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Metastatic
Condition:	Colorectal cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <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 OR <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have received an initial authority prescription for cetuximab for first-line treatment of RAS wild-type metastatic colorectal cancer,</p> <p>AND</p> <p>Patient must not have progressive disease,</p> <p>AND</p> <p>The treatment must be in combination with first-line chemotherapy,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised anti-EGFR antibody therapy for this condition.</p>
Administrative advice	<p>Note Special Pricing Arrangements apply.</p> <p>Note Cetuximab is not PBS-subsidised for use in combination with another anti-</p>

	<p>EGFR antibody or in combination with an anti-VEGF antibody.</p> <p>Note Cetuximab is not PBS-subsidised when chemotherapy partners are switched whilst maintaining an anti-EGFR antibody backbone in the face of progressive disease.</p> <p>Note The treatment must not exceed a single course of therapy with cetuximab for metastatic colorectal cancer in a patient's lifetime.</p>
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8.2 Amend existing cetuximab second-line metastatic CRC listings as follows (recommended amendments in bold type face):

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

Category / Program	Section 100 (Efficient Funding of Chemotherapy (EFC)) for Public/Private Hospital Use
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Metastatic
Condition:	Colorectal cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <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 OR <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have K-RAS wild-type metastatic colorectal cancer,</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less,</p> <p>AND</p> <p>The condition must have failed to respond to first-line chemotherapy,</p> <p>AND</p> <p>The treatment must be in combination with irinotecan-based chemotherapy; OR</p> <p>The treatment must be as monotherapy,</p> <p>AND</p>

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	The treatment must be the sole PBS-subsidised anti-EGFR antibody therapy for this condition.
Prescriber Instructions	<p>Patients who have progressive disease on panitumumab are not eligible to receive PBS-subsidised cetuximab.</p> <p>Patients who have developed intolerance to panitumumab of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised cetuximab.</p>
Administrative advice	<p>Note Special Pricing Arrangements apply.</p> <p>Note Cetuximab is not PBS-subsidised for use in combination with oxaliplatin-based therapies another anti-EGFR antibody or in combination with an anti-VEGF antibody.</p>

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
CETUXIMAB				
Injection, 100 mg/20 mL	550 mg	11	Erbitux	SG
Injection, 500 mg/100 mL				

Category / Program	Section 100 (Efficient Funding of Chemotherapy (EFC)) for Public/Private Hospital Use
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Metastatic
Condition:	Colorectal cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <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 OR <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have received an initial authority prescription for cetuximab for treatment of K-RAS wild-type metastatic colorectal cancer after failure of first-line chemotherapy,</p> <p>AND</p> <p>Patient must not have progressive disease,</p> <p>AND</p> <p>The treatment must be in combination with irinotecan-based chemotherapy; OR</p> <p>The treatment must be as monotherapy,</p>

	<p>AND</p> <p>The treatment must be the sole PBS-subsidised anti-EGFR antibody therapy for this condition.</p>
Prescriber Instructions	<p>Patients who have progressive disease on panitumumab are not eligible to receive PBS-subsidised cetuximab.</p> <p>Patients who have developed intolerance to panitumumab of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised cetuximab.</p>
Administrative advice	<p>Note Special Pricing Arrangements apply.</p> <p>Note Cetuximab is not PBS-subsidised for use in combination with oxaliplatin-based therapies another anti-EGFR antibody or in combination with an anti-VEGF antibody.</p> <p>Note Cetuximab is not PBS-subsidised when chemotherapy partners are switched whilst maintaining an anti-EGFR antibody backbone in the face of progressive disease.</p> <p>Note The treatment must not exceed a single course of therapy with cetuximab for metastatic colorectal cancer in a patient's lifetime.</p>

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

Merck Serono is delighted to receive a positive recommendation from the PBAC and looks forward to both cetuximab and bevacizumab being listed on the PBS in all lines of treatment.