

7.5 PANITUMUMAB, injection, 100 mg/5 mL and 400 mg/20 mL, Vectibix[®], Amgen Australia Pty Ltd.

1 Purpose of Application

- 1.1 To request that the current Section 100 (Efficient Funding of Chemotherapy Program) Authority Required listing of panitumumab in the treatment of later-line metastatic colorectal cancer (mCRC) be amended to:
- a) include first-line treatment; and
 - b) be limited to patients whose tumours have rat sarcoma proto-oncogene wild type (RAS WT) status rather than Kirsten RAS wild type (KRAS WT) status.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Amt.	№.of Rpts	Proprietary Name and Manufacturer	
PANITUMUMAB Solution for IV infusion 100 mg in 5 mL & 400 mg in 20 mL	720 mg	11	Vectibix [®]	AMGEN

- 2.1 The two requests of the re-submission are both consistent with recent changes in approvals by the TGA and the European Medicines Agency (EMA). The current TGA indications for panitumumab (product information amended 26 May 2014) and cetuximab (product information amended 3 April 2014) both include first-line treatment and also are limited to mCRC patients with RAS WT tumours. The intention of the request regarding RAS is that anti-EGFR antibodies (cetuximab and panitumumab) should only be used in patients with RAS WT tumours.

For more detail on PBAC's view, see section 7 "PBAC outcome" and section 8 "Recommended listing"

3 Background

- 3.1 Panitumumab is TGA registered for treatment of patients with wild-type RAS metastatic colorectal cancer as first line therapy in combination with FOLFOX, as second line therapy in conjunction with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy, and as monotherapy in patients after failure of standard chemotherapy.
- 3.2 This is the fourth submission for panitumumab for consideration by the PBAC.
- 3.3 In November 2008, the PBAC rejected a submission for the treatment of KRAS WT mCRC after failure of treatment with chemotherapy on the basis of uncertainty regarding the extent of clinical benefit over best supportive care (BSC).
- 3.4 In March 2013, the PBAC recommended listing of panitumumab in the later-line treatment of KRAS WT mCRC, but rejected a request for first-line treatment of patients for whom treatment with bevacizumab is unsuitable.
- 3.5 In November 2013, the PBAC recommended a revised cost-minimisation basis for listing of panitumumab in the later-line treatment of KRAS WT mCRC. However, the

PBAC noted with concern the emerging data on a reduced treatment effect of panitumumab (and cetuximab) in patients with mutations in the *RAS* family other than in *KRAS* exon 2.

- 3.6 Existing *KRAS* mutation testing focuses on detecting mutations on *KRAS* exon 2, although neither the existing MBS item descriptor nor the PBS restriction excludes testing for *KRAS* mutations on *KRAS* exons 3 or 4. This re-submission to the PBAC is being coordinated with an application (Application 1363) to the July/August 2014 MSAC meeting requesting expansion of the existing MBS item descriptor in order to determine eligibility for panitumumab or cetuximab (regardless of line of therapy). The intention is to also test for mutations on *NRAS* exons 2, 3, or 4, although the request would not exclude testing for *HRAS* mutations.
- 3.7 From the 2011 EMA Assessment Report for panitumumab, the prevalence of these *RAS* mutations is: *KRAS* exon 2 (42.4%), *KRAS* exon 3 (4.5%), *KRAS* exon 4 (5.5%), *NRAS* exon 2 (3.8%), *NRAS* exon 3 (3.2%), *NRAS* exon 4 (not determinable), and *HRAS* (<1%).

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. Panitumumab and cetuximab are currently PBS-listed for the later-line treatment of mCRC patients with *KRAS* WT tumours. Bevacizumab is not PBS-subsidised for later-line treatment.

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

5 Comparator

- 5.1 The appropriate main comparators for first-line treatment of mCRC are chemotherapy alone or chemotherapy plus bevacizumab. Cetuximab (another anti-EGFR antibody) is another relevant comparator should the same listing be sought.

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 discussed how the drug would be used in practice and addressed other matters in response to the Committee's questions. The clinician expressed the view that panitumumab and cetuximab exerted a class effect, and that clinicians would prefer to have both these medicines available to be used in sequence with each other for a minority of patients. The clinician also expressed the view that anti-EGFR antibodies and combination chemotherapy used as first line agents for *KRAS* WT patients were at least as effective as bevacizumab and combination chemotherapy. In this regard, the clinician mentioned the CALGB/SWOG study.

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

Consumer comments

6.2 No consumer comments were received for this item.

Clinical trials

6.3 The table below identifies the two direct randomised trials (PRIME and PEAK) that support the request to list panitumumab as first-line treatment. Six additional randomised trials (three for cetuximab as first-line treatment: FIRE-3, OPUS and COIN; and three for panitumumab as later-line treatment: Study 181, Study 408 and PICCOLO) are also relevant to support the request for eligibility to be determined on the basis of RAS WT rather than KRAS WT.

Trial ID	Protocol title/ publication title	Publication citation
Panitumumab + FOLFOX versus FOLFOX alone		
PRIME	<p>Amgen Inc: Clinical Study Report: 20050203 A Randomised, Multicenter, Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Oxaliplatin/5-fluorouracil/leucovorin to the Efficacy of Oxaliplatin/5-fluorouracil/leucovorin Alone in Patients with Previously Untreated Metastatic Colorectal Cancer.</p> <ul style="list-style-type: none"> • Data cut-off date 30 September 2008 (primary analysis of PFS) • Data cut-off date 28 August 2009 (primary analysis of OS) • Data cut-off date 19 January 2012 (final descriptive analyses) • Data cut-off date 15 April 2013 (RAS/BRAF supplement) <p>Douillard, J. Y., S. Siena, et al. "Randomised, Phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) Versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: The PRIME study."</p> <p>Douillard JY, Oliner KS, Siena S et al. "Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer."</p> <p>Bennett, L., Z. Zhao, et al. "Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first-or second-line treatment."</p>	<p>March 2010 Jun 2010 January 2012 April 2013</p> <p><i>Journal of Clinical Oncology</i>, 2010; 28(31):4697-4705</p> <p><i>New England Journal of Medicine</i>, 2013; 369:1023-34.</p> <p><i>British Journal of Cancer</i>, 2011a; 105(10):1495-1502.</p>
Panitumumab + FOLFOX versus bevacizumab + FOLFOX		
PEAK	<p>Amgen Inc: Clinical Study Report: 20070509 A Randomized, Multicenter, Phase 2 study to compare the efficacy of panitumumab in combination with mFOLFOX6 to the efficacy of bevacizumab in combination with mFOLFOX6 in patients with previously untreated, KRAS wild-type, unresectable, metastatic colorectal cancer. Protocol Number 20070509.</p> <p>Schwartzberg, L. S. and V. J. Wagner : "PEAK: A randomised phase II study to compare the efficacy of panitumumab plus mFOLFOX6 to bevacizumab plus mFOLFOX6 in patients (pts) with previously untreated, unresectable metastatic colorectal cancer (mCRC) expressing wild-type KRAS."</p>	<p>December 2012 and July 2013</p> <p><i>Journal of Clinical Oncology</i>, 2013; 31(15). (Abstract)</p>

Source: Table B.2.3, pp5-7, Section B of the re-submission.

6.4 The key features of the two trials involving panitumumab as first-line treatment are summarised in the table below.

Trial	N	Design/approx. duration of follow-up	Risk of bias/confounding	Patient population ^A	Outcome(s)	Use in model
Direct comparison: panitumumab + FOLFOX vs FOLFOX alone						
PRIME ITT (Unselected)	1183	R, OL Duration NR	PFS: low risk of bias. OS: low risk of confounding despite post-progression therapy. ^B	First-line <i>RAS</i> WT mCRC	PFS, OS	Used
<i>RAS</i> WT subgroup (pre-specified)	512	95 weeks pmab, 77 weeks FOLFOX	Estimation of adverse events: high risk of bias due to open label design			
Direct comparison: panitumumab + FOLFOX vs bevacizumab + FOLFOX						
PEAK ITT: <i>KRAS</i> WT (Exon 2)	285	R, OL 60 weeks for pmab or bev	PFS: low risk of bias. OS: high risk of confounding due to post-progression therapy. ^C	First-line <i>RAS</i> WT mCRC	PFS, OS	Used
<i>RAS</i> WT subgroup (pre-specified)	170	90 weeks for pmab or bev	Estimation of adverse events: high risk of bias due to open label design.			

^A The *RAS* (*KRAS* and *NRAS*) wild type (WT) subgroup data sets in the trials do not represent a randomised comparison. However, although patients were not randomised or stratified by these subgroups, baseline data, for each treatment arm, were presented for these subgroups which indicate demographic and clinical characteristics were fairly equally distributed across compared treatments thus minimising the potential for confounding.

^B Although █% of patients in the FOLFOX alone arm (*RAS* WT subgroup) received panitumumab or cetuximab as post-progression therapy, this option reflects the current PBS listings of these medicines. Also, although both arms received bevacizumab as post-progression therapy, which does not reflect current PBS listing of this medicine, the proportions were similar across the arms (█% in the FOLFOX alone arm and █% in the panitumumab + FOLFOX arm).

^C Although █% of patients in the bevacizumab + FOLFOX arm (*RAS* WT subgroup) received panitumumab or cetuximab as post-progression therapy, this option reflects the current PBS listings of these medicines. However █% of patients in the panitumumab + FOLFOX arm received bevacizumab as post-progression therapy, which does not reflect current PBS listing of this medicine, and biases the OS results in favour of first-line panitumumab compared to the Australian setting.

KRAS WT Exon 2=No mutation in *KRAS* exon 2; mCRC=Metastatic colorectal cancer; Pmab=panitumumab; Bev=Bevacizumab; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; NR=Not reported.

Source: compiled during the evaluation from the main body of the re-submission and the PEAK and PRIME clinical study reports.

- 6.5 The two trials are not exchangeable. For example, participants eligible to be enrolled in PRIME, but not PEAK, had a worse prognosis because they could have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 and be at increased risk of bleeding with bevacizumab. However, panitumumab and FOLFOX should have a more favourable comparison against FOLFOX alone (PRIME) than against bevacizumab and FOLFOX (PEAK), because adding bevacizumab should be expected to improve health outcomes over FOLFOX alone.

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

Comparative effectiveness

First-line panitumumab treatment trials

Progression-free survival (PFS), by *RAS* subgroup, across the direct randomised trials

Trial	KRAS Exon 2 WT population ^A		RASWT population (KRAS and NRAS Exons 2/3/4)		KRAS Exon 2 WT, RAS M+ population	
	Pmab + FOX	FOX	Pmab + FOX	FOX	Pmab + FOX	FOX
PRIME						
N	325	331	259	253	51	57
Median PFS, months [∞] (95% CI)	10.0 (9.3, 11.4)	8.6 (7.5, 9.5)	10.8 (9.4, 12.9)	8.6 (7.3, 9.6)	7.4 (5.5, 9.4)	8.1 (7.2, 12.6)
Difference in PFS	+1.4		+2.2		-0.7	
HR (95% CI)	0.80 (0.67, 0.95)		0.73 (0.60, 0.88)		1.37 (0.90, 2.10)	
Interaction test RASWT vs KRAS Exon 2 WT, RAS M+	p = 0.0079					
PEAK						
N	142	143	88	82	24	27
Median PFS, months [§] (95% CI)	10.9 (9.7, 12.8)	10.1 (9.0, 12.0)	13.0 (10.9, 15.1)	10.1 (9.0, 12.7)	8.4 (6.5, 10.7)	8.8 (7.3, 11.2)
Difference in PFS	+0.8		+2.9		-0.4	
HR [95% CI]	0.84 (0.64, 1.11)		0.66 (0.46, 0.95)		1.13 (0.63, 2.05)	

^A This is a prespecified subgroup population for the PRIME trial and the ITT population for the PEAK trial.

[∞]Final analysis – Data cut-off August 2010

[§]Updated analysis – Data cut-off 3 January 2013.

^ΔThe interaction test for the 2012 data cut-off (which compared the RASWT hazard ratio [redacted] and the KRAS WT, RAS mutant hazard ratio [redacted] was statistically significant (p=0.0476).

A hazard ratio <1.0 favours panitumumab. Bev = bevacizumab; Pmab = panitumumab. CI = confidence interval; KRAS = Kirsten rat sarcoma-2 viral oncogene; PFS = progression-free survival (Investigator Assessment); RAS WT (Pre-specified subgroup): rat sarcoma viral oncogene homolog wild type.

Overall survival (OS), by RAS subgroup, across the direct randomised trials

Trial	KRAS Exon 2 WT population ^A		RASWT population (KRAS/NRAS Exons 2/3/4)		KRAS Exon 2 WT, RAS M+ population	
	Pmab + FOX	FOX	Pmab + FOX	FOX	Pmab + FOX	FOX
PRIME[^]						
N	325	331	259	253	51	57
Median OS, months (95% CI)	23.9 (20.3, 27.7)	19.7 (17.6, 22.7)	25.8 (21.7, 29.7)	20.2 (17.6, 23.6)	17.1 (10.8, 19.4)	17.8 (13.0, 23.2)
Difference in OS	+4.2		+5.6		-0.7	
HR (95% CI)	0.88 (0.73, 1.06)		0.77 (0.64, 0.94)		1.39 (0.91, 2.13)	
Interaction test RASWT vs KRAS Exon 2 WT, RAS M+	p = 0.0128					
PEAK[*]						
N	142	143	88	82	24	27
Median OS, months (95% CI)	34.2 (26.6, NE)	24.3 (21.0, 29.2)	41.3 (28.8, 41.3)	28.9 (23.9, 31.3)	27.0 (15.1, NE)	16.6 (13.3, 21.6)
Difference in OS	+9.9		+12.4		+10.4	
HR (95% CI)	0.62 (0.44, 0.89)		0.63 (0.39, 1.02)		0.41 (0.19, 0.87)	

^A This is a prespecified subgroup population for the PRIME trial and the ITT population for the PEAK trial.

[^]Data cutoff for KRAS Exon 2 WT: 02 Aug 2010; and for RASWT and KRAS Exon 2 WT, RAS M+: 24 JAN 2013

^{*}Data cutoff 03 Jan 2013

NE=Not estimable; A hazard ratio <1.0 favours panitumumab. Bev = bevacizumab; Pmab = panitumumab. CI = confidence

interval; *KRAS* = Kirsten rat sarcoma-2 viral oncogene; OS=Overall survival; *RAS* WT (Pre-specified subgroup): rat sarcoma viral oncogene homolog wild type.

- 6.6 The results of both trials are mostly similar: superiority of first-line panitumumab with FOLFOX over both FOLFOX alone and bevacizumab + FOLFOX in the *KRAS* WT (exon 2) populations, separating to a trend to a greater superiority in the *RAS* WT subgroups of these populations, and to inferiority in the subgroup of patients with *RAS* mutations other than in exon 2 *KRAS* (labelled *KRAS* WT, exon 2 *RAS* M+). Tests of interaction across these subgroups and the treatment effect were significant for the PRIME trial, but not in the smaller PEAK trial. These different results across subgroups are biologically plausible.
- 6.7 One result that is not biologically plausible is the numerically improved effect for OS in the *KRAS* WT (exon 2), *RAS* mutant subgroup from the PEAK trial. Results from this small subgroup should be interpreted with caution for two reasons:
- First, there are imbalances between the panitumumab + FOLFOX versus bevacizumab + FOLFOX treatment arms in a number of baseline disease characteristics, such as the mean duration since diagnosis of primary tumour (■■■ months vs ■■■ months for panitumumab + FOLFOX vs bevacizumab + FOLFOX) and metastatic disease (■■■ months vs ■■ months, respectively), number of sites of metastatic disease (■■■■% vs ■■■%) and the total number of target lesions (■■ vs ■■). Thus, patients in the bevacizumab + FOLFOX treatment arm at baseline would appear to have a worse prognosis, irrespective of treatment allocation;
 - Second, the proportion of cross over in this subgroup is unknown – it was not provided in the re-submission or described in the clinical study report. Patients with *RAS* mutant tumours not responding to panitumumab could have benefited from cross over upon progression to an active bevacizumab treatment arm, hence potentially experiencing additional OS benefit. *RAS* mutant patients in the bevacizumab treatment arm, crossing over to treatment with panitumumab, are not likely to respond to panitumumab and hence would not experience any additional OS benefit.
- 6.8 Patients with an ECOG performance status of 2 (PFS HR=1.69; 95% CI: 0.75, 3.82 and OS HR=1.34; 95% CI: 0.63, 2.89) or who were ≥75 years of age (PFS HR=1.21; 95% CI: 0.62, 2.38) favoured the FOLFOX alone arm over panitumumab + FOLFOX arm in the *RAS* WT subgroup of the PRIME trial, at least for the 2008 data cut-off PFS analysis and the 2009 data cut-off OS analysis. The wide confidence intervals suggest uncertainty in the point estimate as the analysis in this small subgroup (N=16 in each arm for ECOG 2) appears under-powered. The Pre-Sub-Committee Response (PSCR, p1) accepts that the PBS restriction might be limited to ECOG 0 or 1, noting that this would be consistent with the existing PBS listing of bevacizumab in mCRC.
- 6.9 The OS results of the PRIME trial have a low risk of confounding by cross-over when applied to the Australian PBS setting. The greater risk of confounding due to cross-over to post-progression bevacizumab in the first-line panitumumab treatment arm might explain the apparent greater effect on OS in the PEAK trial than in the PRIME trial. The lack of exchangeability across the two trials might explain the apparent similarity of effect on PFS in the PEAK trial than in the PRIME trial, even though the addition of bevacizumab to FOLFOX in the PEAK trial would be expected to be more effective than FOLFOX alone in the PRIME trial.
- 6.10 The ESC discussed the possibility that the extent of superiority reported in the PEAK trial for panitumumab + FOLFOX over bevacizumab + FOLFOX may be

overestimated. As discussed at the hearing, other larger comparisons of anti-EGFR antibodies and bevacizumab in the first-line setting of mCRC, such as CALGB/SWOG 80405, have not yet fully reported, [REDACTED]

Eligibility to be determined on the basis of RAS WT rather than KRAS WT

Progression-free survival by RAS subgroups from additional randomised trials for first-line cetuximab and later-line panitumumab

Trial	KRAS Exon 2 WT population		RASWT population (KRAS and NRAS Exons 2/3/4)		KRAS Exon 2 WT, RAS M+ population			
First-line treatment - cetuximab								
FIRE-3	Cmab + FIRI	Bev + FIRI	Cmab + FIRI	Bev + FIRI	Cmab + FIRI	Bev + FIRI		
N	297	295	171	171	34	31		
Median PFS, months	10.0 (8.8, 10.8)	10.3 (9.8, 1.3)	10.4 (9.5, 12.2)	10.2 (9.3, 11.5)	6.1 (5.3, 8.5)	12.2 (9.7, 13.9)		
Difference in PFS HR (95% CI)	-0.3 1.06 (0.88, 1.26)		+0.2 0.93 (0.74, 1.17)		-6.1 2.22 (1.28, 3.86)			
OPUS	Cmab + FOX	FOX	Cmab + FOX	FOX	Cmab + FOX	FOX		
N	82	97	36	46	17	19		
Median PFS, months	8.3 (7.2, 12.0)	7.2 (5.6, 7.4)	12.0 (7.7, NE)	5.8 (4.5, 7.5)	7.3 (3.4, 8.3)	7.4 (6.2, 10.3)		
Difference in PFS HR (95% CI)	+1.1 0.57 (0.38, 0.86)		+6.2 0.43 (0.21, 0.88)		-0.1 1.02 (0.41, 2.55)			
COIN (KRAS WT Exons 2,3)	Cmab + OxF	OxF	<i>Not provided in Maughan et al (2011) (Maughan, 2011 #138 but authors note that there was no evidence of PFS benefit seen in any of the genetically defined (RAS and RAF) subgroups.</i>					
N	362	367						
Median PFS, months	8.6	8.6						
Difference in PFS HR (95% CI)	0.07 0.96 (0.82, 1.12)							
Later-line treatment - panitumumab								
Study 181	Pmab + FIRI	FIRI	Pmab + FIRI	FIRI	Pmab + FIRI	FIRI		
N	303	294	204	211	61	46		
Median PFS, months	5.9 (5.5, 6.7)	3.9 (3.7, 5.3)	6.4 (5.5, 7.4)	4.4 (3.7, 5.5)	3.7 (2.3, 5.8)	3.7 (2.8, 5.1)		
Difference in PFS HR (95% CI)	+2.0 0.73 (0.59, 0.90)		+2.0 0.70 (0.54, 0.90)		0.0 0.90 (0.56, 1.42)			
Study 408	Pmab + BSC	BSC	Pmab + BSC	BSC	Pmab + BSC	BSC		
N	124	119	72	61	11	11		
Median PFS (weeks)	12.3 (8.3, 16.1)	7.3 (7.0, 7.7)	12.3 (8.9, 22.9)	6.9 (6.0, 7.4)	7.1 (6.1, 8.0)	7.6 (3.9, 8.1)		
Difference in PFS HR (95% CI)	+5.0 0.45 (0.34, 0.59)		+5.4 0.39 (0.27, 0.56)		-0.5 0.81 (0.29, 2.26) [§]			
PICCOLO								
	KRAS WT (Exon 2,3)		WT: KRAS (Exon 2,3,4), NRAS (Exon 2,3), BRAF, and PIK3CA		KRAS WT (Exon 2,3), KRAS MT (Exon 4)		KRAS WT (Exon 2,3), NRAS MT (Exon 2,3)	
	Pmab + Iri	Iri	Pmab + Iri	Iri	Pmab + Iri	Iri	Pmab + Iri	Iri

N	230	230	160	163	9	8	19	10
PFS HR (95% CI)	0.78 (0.64, 0.95)		0.68 (0.53, 0.86)		0.56 (0.13, 2.48)		1.08 (0.45, 2.56)	
p-value	p=0.015		p-value NR		p-value NR		p-value NR	

Later-line treatment - cetuximab

The CAPRI study and a retrospective cohort analysis by De Rooke et al (De Roock, 2010 #139) do not provide published outcome data by RAS status comparing cetuximab with a comparator arm. Single cetuximab treated cohort data do not allow an assessment of the extent of treatment effect variation independent of a prognostic effect.

^{oo} *Reproduced from Peeters et al (2013) and Table C.3.10, p15 of the re-submission. Differences in median PFS not provided. This interaction test lacked adequate statistical power and PFS benefit favoured the panitumumab arm for patients with KRAS and NRAS WT tumours compared to patients with KRAS WT, NRAS mutant tumours.*

FIRI=FOLFIRI; FOX=FOLFOX; Cmab=cetuximab; Pmab=Panitumumab; Bev=Bevacizumab; Iri = Irinotecan; OxF = Oxaliplatin and fluoropyrimidine; BSC = Best supportive care; NR=Not reported.

Sources: Section C of the re-submission, the European assessment reports for panitumumab and cetuximab and study publications for panitumumab and cetuximab.

Overall survival by RAS subgroups from additional randomised trials for first-line cetuximab and later-line panitumumab (where possible, the most updated OS data corresponding to the most recent cut-off date have been sourced from the available study reports and publications)

Trial	KRAS Exon 2 WT population		RASWT population (KRAS/NRAS Exons 2/3/4)		KRAS Exon 2 WT, RAS M+ population	
	First-line treatment - cetuximab					
FIRE-3	Cmab + FIRI	Bev + FIRI	Cmab + FIRI	Bev + FIRI	Cmab + FIRI	Bev + FIRI
N	297	295	171	171	34	31
Median OS, months (95% CI)	28.7 (24.0, 36.6)	25.0 (22.7, 27.6)	33.1 (24.5, 39.4)	25.6 (22.7, 28.6)	16.4 (15.9, 27.6)	20.6 (17.0, 28.4)
Difference in OS HR (95% CI)	+3.7 0.77 (0.62, 0.96)		+7.5 0.70 (0.53, 0.92)		-4.2 1.20 (0.64, 2.28)	
OPUS	Cmab + FOX	FOX	Cmab + FOX	FOX	Cmab + FOX	FOX
N	82	97	36	46	17	19
Median OS, months (95% CI)	22.8 (19.3, 25.9)	18.5 (16.4, 22.6)	20.7 (18.3, 26.8)	17.8 (12.4, 23.9)	14.8 (8.5, 26.3)	17.8 (15.3, NE)
Difference in OS HR (95% CI)	+4.3 0.86 (0.60, 1.22)		+2.9 0.83 (0.49, 1.41)		-3.0 1.41 (0.62, 3.2)	
COIN	KRAS WT (Exon 2,3)		KRAS WT (Exon 2,3), NRAS WT (Exon 2,3) and BRAF WT		KRAS WT (Exon 2,3), NRAS WT (Exon 2,3), BRAF MT	
	Cmab + OxF	OxF	Cmab + OxF	OxF	Cmab + OxF	OxF
N	362	367	292	289	366	340
Median OS, months (IQR)	17.0 (9.4, 30.1)	17.9 (10.3, 29.2)	19.9 (NR)	20.1 (NR)	12.7 (NR)	14.4 (NR)
Difference in OS HR (95% CI)	-0.9 1.04 (0.87, 1.23)		0 1.02 (0.83, 1.24)		-1.7 1.00 (0.85, 1.18)	

Later-line treatment – panitumumab						
Study	KRASWT (Exon 2)		RASWT		KRAS Exon 2 WT, RAS MT	
	Study 181	Pmab + FIRI	FIRI	Pmab + FIRI	FIRI	Pmab + FIRI
N	303	294	204	211	61	46
Median OS, months (95% CI)	14.5 (13.0, 16.0)	12.5 (11.2, 14.2)	16.2 (14.5, 19.7)	13.9 (11.9, 16.1)	11.3 (8.3, 13.1)	9.2 (7.0, 12.9)
Difference in OS HR (95% CI)	+2.0 0.73 (0.59, 0.90)		+2.3 0.69 (0.54, 0.90)		+2.1 0.89 (0.56, 1.42)	
Study 408	Pmab + BSC	BSC	Pmab + BSC	BSC	Pmab + BSC	BSC

N	124	119	72	61	11	11		
Median OS (months) (95% CI)	8.1 (6.3, 9.4)	7.6 (6.2,8.8)	8.1 (6.3, 9.4)	7.5 (5.6, 9.2)	6.2 (2.3, 6.8)	5.2 (3.9, 13.7)		
Difference in OS HR (95% CI)	+0.5 0.99 (0.75, 1.30) ^A		+0.6 1.03 (0.71, 1.48)		+1.0 0.96 (0.37, 2.51)			
PICCOLO	KRAS WT (Exon 2,3)		WT: KRAS (Exon 2,3,4), NRAS (Exon 2,3), BRAF, and PIKC3A		KRAS WT (Exon 2,3), KRAS MT (Exon 4)		KRAS WT (Exon 2,3), NRAS MT (Exon 2,3)	
	Pmab + Iri	Iri	Pmab + Iri	Iri	Pmab + Iri	Iri	Pmab + Iri	Iri
N	230	230	160	163	9	8	19	10
OS HR (95% CI)	1.01 (0.83, 1.23)		0.92 (0.73, 1.16)		1.73 (0.45, 6.58)		1.97 (0.83, 4.67)	
p-value	p=0.91		p-value NR		p-value NR		p-value NR	
Later-line treatment – cetuximab								
<i>Only single cetuximab treated cohort data are currently available.</i>								

^A 76% of KRAS WT (Exon 2) patients randomised to BSC were treated with panitumumab post progression.

NE = Not estimable; IQR = Interquartile range; FIRI=FOLFIRI; FOX=FOLFOX; Cmab=cetuximab; Pmab=panitumumab; Bev=Bevacizumab; Iri=Irinotecan; OxF=Oxaliplatin and fluoropyrimidine; BSC = Best supportive care; NR=Not reported.

Sources: Section C of the re-submission, *the European assessment reports for panitumumab and cetuximab and study publications for panitumumab and cetuximab.*

6.11 In November 2013, PBAC and MSAC identified three questions which needed to be addressed in relation to the request for RAS testing:

- Is the identified effect of RAS mutation status (in predicting a reduced treatment effect) operating as a class effect across anti-EGFR antibodies, i.e., does it similarly affect both panitumumab and cetuximab?

The ESC considered that particularly for first-line treatment, the effect is most likely operating as a class effect across anti-EGFR antibodies. The clinician expert at the hearing also considered the two drugs should be regarded as a class.

- Is this effect consistent irrespective of the chemotherapy partner with the anti-EGFR antibody, including anti-EGFR antibody used as monotherapy?

The ESC advised that particularly with reference to the range of comparators (to which the anti-EGFR antibody was added in the treatment arm in six of the eight trials presented; it replaced bevacizumab in the other two trials), the effect appears consistent irrespective of the chemotherapy partner (e.g. oxaliplatin or irinotecan) or use as monotherapy.

- Is this effect consistent across all lines of therapy? Anti-EGFR antibodies compete with more effective alternatives in earlier lines of therapy than in later lines of therapy, which may affect the consequences of this effect for comparisons across lines of therapy.

The ESC advised that the effect appears consistent across all lines of therapy, although some extrapolation is required in the absence of data for later-line cetuximab use.

6.12 The ESC noted some limitations with respect to the data presented in the above tables, including:

- other than in the PRIME and PEAK trials, the RAS mutation subgroups were not necessarily pre-specified, and tests for interaction were not provided;
- the absence of baseline data by treatment arm for some of the RAS mutation subgroups hinders assessment of other potential confounders; and
- some of the subgroups were small, especially for the KRAS exon 2 WT, RAS M+ subgroup.

- 6.13 The ESC noted that these results were further supported by the recently released subgroup results of CRYSTAL, which compared first-line cetuximab added to FOLFIRI with FOLFIRI alone. As foreshadowed by PBAC and MSAC in November 2013, these findings support urgent amendments to the relevant PBS restrictions for existing and proposed PBS restrictions for panitumumab and cetuximab, coordinated with corresponding amendments to the MBS item descriptors for mutation testing.

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

Comparative harms

- 6.14 In relation to serious adverse events (AEs) reported in the PRIME and PEAK trials:
- there were more Grade ≥ 3 adverse events (any or drug related) in the panitumumab + FOLFOX arm compared to either FOLFOX alone or compared to bevacizumab + FOLFOX (a difference of approximately 15%);
 - in the PRIME trial, the panitumumab + FOLFOX arm had a higher rate of serious AEs (12% difference) and discontinuations (11% difference) than the FOLFOX alone treatment arm;
 - in the PEAK trial, drug-related discontinuations were slightly higher in the bevacizumab arm than the panitumumab arm; and
 - safety data were similar across the *RAS* WT and *KRAS* WT (exon 2) subgroups.
- 6.15 The PEAK trial excluded patients with CNS metastases or with a significant bleeding risk given the known increased risk of haemorrhage associated with bevacizumab.

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

Benefits/harms

- 6.16 The benefits and harms from panitumumab + FOLFOX treatment are summarised below for the requested first-line treatment of mCRC in the requested eligible population (*RAS* WT subgroup).

RAS WT subgroup (no mutations on *KRAS* and *NRAS* Exons 2/3/4): Summary of comparative benefits and harms for panitumumab + FOLFOX and the comparators 1) bevacizumab + FOLFOX and 2) FOLFOX alone

Benefits				
PRIME ^Δ				
Outcome	Panitumumab + FOLFOX	FOLFOX alone	Absolute difference (months) (panitumumab arm minus comparator arm)	HR (95% CI)
Median PFS, mths, (95% CI)	10.8 (9.4, 12.9)	8.6 (7.3, 9.6)	+2.2	0.73 (0.60, 0.88)
Median OS, mths, (95% CI)	25.8 (21.7, 29.7)	20.2 (17.6, 23.6)	+5.6	0.77 (0.64, 0.94)

PEAK [*]				
Outcome	Panitumumab + FOLFOX	Bevacizumab + FOLFOX	Absolute difference (months) (panitumumab arm minus comparator arm)	HR (95% CI)
Median PFS, mths, (95% CI)	13.0 (10.9, 15.1)	10.1 (9.0, 12.7)	+2.9	0.66 (0.46, 0.95)
Median OS, mths, (95% CI)	41.3 (28.8, 41.3)	28.9 (23.9, 31.3)	+12.4	0.63 (0.39, 1.02)

Harms

PRIME					
Panitumumab + FOLFOX	Bevacizumab + FOLFOX	RR (95% CI)	Patients with AEs/100		RD/100 patients (95% CI)
			Panitumumab + FOLFOX	FOLFOX alone	
Any Grade 3 or higher adverse event					
231/256	191/250	1.18 (1.09, 1.28)	90.2	76.4	14.0 (7.0, 20.0)
Any serious adverse event					
111/256	92/250	1.18 (0.95, 1.46)	43.4	36.8	6.6 (-2.0, 15.0)
Grade 3 or higher drug-related^β adverse event					
216/256	162/250	1.30 (1.18, 1.44)	84.4	64.8	20.0 (12.0, 27.0)
Any serious drug-related^β adverse event					
71/256	41/250	1.69 (1.21, 2.37)	27.7	16.4	11.3 (4.0, 19.0)
PEAK					
Panitumumab + FOLFOX	FOLFOX alone	RR (95% CI)	Patients with AEs/100		RD/100 patients (95% CI)
			Panitumumab + FOLFOX	Bevacizumab + FOLFOX	
Any Grade 3 or higher adverse event					
81/86	65/80	1.16 (1.03, 1.30)	94.2	81.3	13.0 (3.0, 23.0)
Any serious adverse event					
37/86	32/80	1.08 (0.75, 1.55)	43.0	40.0	3.0 (-12.0, 18.0)
Any Grade 3 or higher drug-related^β adverse event					
78/86	58/80	1.25 (1.08, 1.45)	90.7	72.5	18.0 (6.0, 30.0)
Any serious drug-related^β adverse event (difference was small ~1%)					

^Δ PRIME median duration of follow-up: Panitumumab + FOLFOX: 95 weeks; FOLFOX: 77 weeks.

* PEAK median duration of follow-up for the WT *RAS* population was approximately 90 weeks

^β The investigator considered there to be a reasonable possibility that the event may have been caused by study drug.

RD = risk difference; RR = risk ratio

Source: compiled during the evaluation from Tables B.6.1-5 of Section B of the Commentary.

- 6.17 On the basis of the head-to-head PRIME trial, the comparison of panitumumab + FOLFOX to FOLFOX alone resulted in:
- approximately 2.2 months gain in median progression-free survival and 5.6 months gain in median overall survival, observed over a median duration of approximately 95 weeks of follow-up;
 - 20 additional patients experiencing a Grade 3 or higher drug-related adverse event for every 100 patients treated.
- 6.18 On the basis of the head-to-head PEAK trial, the comparison of panitumumab + FOLFOX to bevacizumab + FOLFOX resulted in:
- approximately 2.9 months gain in median progression-free survival and 12.4 months gain in median overall survival, observed over a median duration of approximately 90 weeks of follow-up;
 - 18 additional patients experiencing a Grade 3 or higher drug-related adverse event for every 100 patients treated.

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

Clinical claim

- 6.19 For the first-line *RAS* WT mCRC population, the re-submission describes panitumumab + FOLFOX as:
- superior in terms of comparative effectiveness and with "a different safety profile" compared to bevacizumab + FOLFOX; and
 - superior in terms of comparative effectiveness and which "adds a manageable level of toxicity" (or otherwise inferior in terms of comparative safety) over FOLFOX alone.

- 6.20 Each description about comparative effectiveness is supported by the respective randomised trial, however the addition of panitumumab to FOLFOX appears to have an inferior safety profile compared with the addition of bevacizumab to FOLFOX or compared with FOLFOX alone.

Economic analysis – cost-utility

- 6.21 The re-submission presents modelled cost-utility analyses in *RAS* WT mCRC for comparisons of first-line panitumumab + FOLFOX with (1) bevacizumab + FOLFOX, (2) FOLFOX alone, and (3) a weighted combination of these comparators. This is consistent with the claims of superiority presented in the clinical evidence.
- 6.22 The re-submission did not present an economic evaluation of the other request in the re-submission to change the PBS eligibility criteria for panitumumab from *KRAS* WT to *RAS* WT. The ESC advised that such an evaluation would result in dominance for *RAS* WT because this would reduce the proportion of existing patients receiving additional panitumumab resulting in inferior health outcomes, and the increased costs of *RAS* testing would be outweighed by the decreased costs of panitumumab.
- 6.23 The economic model presented in the re-submission compares *RAS* testing for access to anti-EGFR antibody treatment in the first-line setting to *RAS* testing for anti-EGFR antibody treatment in the second-line setting. A comparison is not made to a scenario where *KRAS* testing occurs, although this is current practice.

Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus maximum follow-up of 2.5 years in the PRIME trial. The ESC considered the 10-year time horizon to be appropriate given that █% of patients were alive at a maximum follow up of 6 years.
Outcomes	LYG and QALYs
Methods used to generate results	Markov model (with half cycle correction applied to QALYs, but not costs)
Health states	Seven health states, including: progression-free, progressive disease (active treatment), progressive disease (BSC), attempted resection of metastases, disease-free after resection, disease relapse after resection and dead.
Cycle length	2 weeks
Transition probabilities	PFS and OS from PRIME and disease-free survival and OS from Adam et al (2004)

Note: The model structure depicted is applicable for each modelled comparison.

BSC= best supportive care; LYG= life years gained; OS= overall survival; PFS= progression-free survival; QALY= quality-adjusted life years. Source: Table D.3.1 of the commentary.

- 6.24 The key drivers and their impact on the economic model are presented in the table below.

Key drivers of the model

Description	Method/value	Impact
HR from the PEAK trial used to estimate OS of bevacizumab + FOLFOX from the PRIME trial estimate of OS for panitumumab + FOLFOX	HR=0.663. The PEAK and PRIME trials are not exchangeable because the eligibility criteria differ according to the perceived risks of enrolled patients and the post-progression use of bevacizumab in the panitumumab + FOLFOX arm of the PEAK trial. It may be more appropriate to use survival data from the direct PEAK trial to inform the comparison of panitumumab + FOLFOX vs bevacizumab + FOLFOX.	In model that compares panitumumab + FOLFOX to bevacizumab + FOLFOX: <ul style="list-style-type: none"> • using upper 95% CL: high, favours panitumumab • no impact in model that compares panitumumab + FOLFOX to FOLFOX alone
Weibull fitted treatment effect	$\beta=0.2026$, based on fitted Weibull curve (using the FOLFOX OS survival curve as the reference i.e. = 0).	In model that compares panitumumab + FOLFOX to

Description	Method/value	Impact
parameter (β) for OS		FOLFOX alone: <ul style="list-style-type: none"> • using lower 95% CL: high, favours panitumumab • using upper 95% CL: moderate, favours comparator
Later-line anti-EGFR antibody treatment	All <i>RAS</i> WT patients in the comparator arm are assumed to incur the costs of an anti-EGFR antibody after disease progression. This may not be a reasonable assumption, as current utilisation of cetuximab is lower than expected (DUSC mCRC report, 2013) and neither trial reported this extent of second-line anti-EGFR antibody. It is reasonable to assume post-progression anti-EGFR antibody use in the comparator arm, and it would be consistent to use the proportions reported in the relevant trials.	High, favours panitumumab (both comparisons)
Treatment intensity	█%; estimated from the ratio of observed █ to expected █ panitumumab treatment cycles in <i>RAS</i> WT patients in the PRIME trial; this has been applied to all treatment arms. The treatment duration of █ cycles in <i>RAS</i> WT treated with panitumumab in the PRIME trial has not been verified during the evaluation. An estimate of 15 cycles may be more appropriate, increasing the treatment intensity to █, and for FOLFOX alone, █.	High, favours panitumumab (both comparisons)
Cost of BSC	\$█ per cycle, based on a UK study of breast cancer patients in which outpatient visits accounted for 37.9% of the total monthly cost of BSC. The re-submission assumes Australian patients would likely have █; and so then the cost per cycle (fortnightly) of BSC would equate to: █. This may not be a reasonable approach to estimate the costs of BSC. The PSCR argues that inclusion of a same day palliative care admission per cycle would significantly overestimate the cost of BSC. The model was re-run with a BSC cost of \$█ which the ESC considered to be more plausible.	High, favours panitumumab (both comparisons). This is likely to underestimate the ICER as the duration in BSC is substantially longer in the panitumumab arms of the model compared to the comparator arms.

Source: compiled during the evaluation

6.25 The results of the stepped analyses are presented in the table below. The final result for each of the two cost-utility analyses is presented in Steps 7a (\$45,000/QALY - \$75,000/QALY) gained over FOLFOX alone) and 7b (dominant over bevacizumab + FOLFOX). These results are weighted in Step 8, assuming █% use in patients who would otherwise receive bevacizumab + FOLFOX, and █% who would receive FOLFOX alone.

Results of the stepped economic evaluation

Step and component	Panitumumab + FOLFOX (and first-line <i>RAS</i> testing)	Comparator (and later-line <i>RAS</i> testing)	Increment
Step 1: trial-based estimate (<i>RAS</i> WT patients, comparator = FOLFOX alone)			
Costs	\$█	\$█	\$█
LY	█	█	█
Incremental cost/extra LY gained			\$█
Step 2: modelled estimate that includes costs of resection, later-line treatment and testing (not discounted, 2.5 year time horizon, comparator = FOLFOX alone)			
Costs	\$█	\$█	\$█
LY	█	█	█
Incremental cost/extra LY gained			\$█

Step 3: transformation of outcomes into QALYs and extrapolated outcomes to 10 years (discounted, comparator = FOLFOX alone)			
Costs	\$	\$	\$
QALY			
Incremental cost/extra QALY gained			\$
Step 4: applied prevalence of RAS WT (assumed from that observed in the trial- no change, comparator = FOLFOX alone)			
Costs	\$	\$	\$
QALY			
Incremental cost/extra QALY gained			\$
Step 5a: applied Australian later-line treatment algorithm (costs and outcomes, comparator = FOLFOX alone)			
Costs	\$	\$	\$
QALY			
Incremental cost/extra QALY gained			\$
Step 5b: applied Australian later-line treatment algorithm (costs and outcomes, comparator = bevacizumab + FOLFOX)			
Costs	\$	\$	\$
QALY			
Incremental cost/extra QALY gained			\$
Step 6a: includes costs and outcomes of RAS M+ patients to model outcomes of RAS testing (comparator = FOLFOX alone)			
Costs	\$	\$	\$
QALY			
Incremental cost/extra QALY gained			\$
Step 6b: includes costs and outcomes of RAS M+ patients to model outcomes of RAS testing (comparator = bevacizumab + FOLFOX)			
Costs	\$	\$	\$
QALY			
Incremental cost/extra QALY gained			\$
Step 7a: all tested patients, includes outcomes for false positive and false negative patients, and the cost of testing in the later-line setting in the comparator arm of the model (comparator = FOLFOX alone)			
Costs	\$	\$	\$
QALY			
Incremental cost/extra QALY gained			\$
Step 7b: all tested patients, includes outcomes for false positive and false negative patients, and the cost of testing in the later-line setting in the comparator arm of the model (comparator = bevacizumab + FOLFOX)			
Costs	\$	\$	-\$
QALY			
Incremental cost/extra QALY gained			
Step 8: weighted, assuming % of costs and outcomes from the bevacizumab + FOLFOX model, and % from the FOLFOX alone model			
Costs	\$	\$	\$
QALY			
Incremental cost/extra QALY gained			\$

Source: constructed during the evaluation from Section D.6.1 and D.6.2.1 and Tables D.6-1 and D.6-2, pp32-38 of Section D of the re-submission.

6.26 A key driver of the economic evaluation as demonstrated in moving from Step 4 to Step 5a above is the limited treatment options post-progression costed in % of the proposed panitumumab + FOLFOX arm (chemotherapy alone) compared all patients receiving more costly cetuximab in % of the FOLFOX alone arm. These percentages reflect the extent of post-progression use in the PRIME trial. This flows on to a similar assumption for all patients receiving more costly cetuximab in the bevacizumab + FOLFOX arm in Step 5b (the percentage receiving post-progression therapy not clear, but is likely to reflect the % from the PRIME trial rather than % from the PEAK trial). As the incremental costs are therefore likely to be underestimated for both analyses, the corresponding ICERs are also likely to be underestimated.

- 6.27 The PSCR (p1-2) argues that, on the basis of clinician advice, it is likely that around █% of eligible patients who receive active second-line treatment would receive cetuximab.
- 6.28 The model was re-run to assume costs of cetuximab in █% of modelled patients. The ESC considered that █% is more likely but possibly still an overestimate. It would be more appropriate for these costs of cetuximab to reflect the proportion of patients in the FOLFOX alone arm of the PRIME trial (which generated the corresponding estimate of health outcomes) who actually received post-progression anti-EGFR antibodies █%, using the latest (2010) data cut-off) as a better estimate of the current PBS population, with the remainder of patients progressing on FOLFOX alone receiving FOLFIRI alone. The results of this sensitivity analysis are presented in the table below.

Sensitivity analyses to reflect post-progression therapy in the PRIME trial

	Panitumumab + FOLFOX	FOLFOX alone	Increment
Base case (Step 7a): after first-line FOLFOX: █% cetuximab + FOLFIRI (in those who receive active treatment) [so █% of all patients receive cetuximab + FOLFIRI, █% receive no treatment]			
Costs	\$ █	\$ █	\$ █
QALY	█	█	█
Incremental cost/extra QALY gained			\$ █
Revised: after first-line FOLFOX: █% FOLFIRI alone; █% cetuximab + FOLFIRI (in those that receive active treatment) [so █% of all patients receive cetuximab + FOLFIRI, █% receive FOLFIRI alone, and █% receive no treatment]			
Costs	\$ █	\$ █	\$ █
QALY	█	█	█
Incremental cost/extra QALY gained			\$94,113
	Panitumumab + FOLFOX	Bevacizumab + FOLFOX	Increment
Base case (Step 7b): after first-line bevacizumab + FOLFOX: █% cetuximab + FOLFIRI (in those who receive active treatment) [so █% of all patients receive cetuximab + FOLFIRI, █% receive no treatment]			
Costs	\$ █	\$ █	-\$ █
QALY	█	█	█
Incremental cost/extra QALY gained			█

Revised: after first-line bevacizumab + FOLFOX: █% FOLFIRI alone; █% cetuximab + FOLFIRI (in those that receive active treatment) [so █% of all patients receive cetuximab + FOLFIRI, █% receive FOLFIRI alone, and █% receive no treatment]			
Costs	\$ █	\$ █	\$ █
QALY	█	█	█
Incremental cost/extra QALY gained			\$ █

Source: calculated by re-specifying post-progression costs in the submitted model as indicated.

- 6.29 The approach taken by the re-submission to model survival to inform the comparison of panitumumab + FOLFOX vs bevacizumab + FOLFOX in Step 5b above has unreasonable consequences. The re-submission applies the HRs from the PEAK trial to the modelled survival results of the panitumumab + FOLFOX arm from the PRIME trial rather than from the PEAK trial, to model survival results for bevacizumab + FOLFOX. The ESC noted that applying the HR from the PEAK trial requires a counterintuitive inference of a numerically greater treatment effect for panitumumab + FOLFOX over bevacizumab + FOLFOX than over FOLFOX alone.

Interpretation of these results is hindered by the lack of exchangeability of the two trials and the high risk of bias and relatively small sample size of the PEAK trial. This leads to additional uncertainty in the corresponding ICER for panitumumab + FOLFOX over bevacizumab + FOLFOX, also favouring panitumumab. The ESC advised that it may be more appropriate to base the consideration of the first line listing only on the PRIME-based comparison with FOLFOX alone given the PRIME trial is larger and produces less confounded results than the PEAK trial. The Pre-PBAC response (p2) argues that hazard ratios for outcomes such as PFS and OS are typically regarded as likely to be similar regardless of baseline risk and this is why the hazard ratios from PEAK were used in the economic model to quantify the relative efficacy of the two treatment arms.

- 6.30 Costs following progression after second-line therapy may also be underestimated, both in terms of underestimating the use of third-line chemotherapy and underestimating the per cycle cost of best supportive care (BSC). This favours panitumumab because the model generates a longer time in the post-progression state with panitumumab. The PSCR (p2) increases the BSC per cycle cost of \$[REDACTED] rather than \$[REDACTED] in the base case, which increased the ICER over FOLFOX alone (from \$45,000/QALY - \$75,000/QALY gained) and over bevacizumab + FOLFOX (from dominant to less than \$15,000/QALY gained).
- 6.31 The ESC was concerned that the modelling of mortality benefit of resection with curative intent amounts to double-counting of the extrapolated incremental OS gain, but the extent of any impact of this was unclear.
- 6.32 Univariate sensitivity analyses were presented in the re-submission using upper and lower limits for 63 parameters. A number of the analyses tested ranges that were considered by the re-submission as extreme changes or arbitrary changes (-20%/+25% or -50%/+100%). The ESC agreed with the commentary that, in some instances, the ranges used were inadequate or inappropriate.
- 6.33 The ICER for the comparison of panitumumab + FOLFOX compared to bevacizumab + FOLFOX is sensitive to the upper limit of this HR (ICER approximately more than \$200,000/QALY). The PSCR (p3) argues that this ICER should be interpreted as bevacizumab being inadequately cost effective compared to panitumumab. The ESC interpreted this ICER point estimate to mean that starting with panitumumab + FOLFOX would be both less costly (\$[REDACTED]) and less effective ([REDACTED] QALYs) than starting with bevacizumab + FOLFOX.
- 6.34 The parameters associated with the most uncertainty in the re-specified analyses were changes to the treatment effect parameters for PFS and OS. The ICER increases substantially in the range of \$105,000/QALY - \$200,000/QALY (even when the assumptions with Step 5 are retained in the model) when the upper range for PFS treatment effect is assumed to result in no difference in treatment effect for OS. The ICER is additionally most sensitive to the administration adjustment parameter (treatment intensity in line 1, with the base case favouring first-line panitumumab) and second-line progression-free survival in RAS WT patients treated with cetuximab.
- 6.35 The ESC agreed that using a weighted ICER required acceptance of the counterintuitive ICER for panitumumab + FOLFOX over bevacizumab + FOLFOX.

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

Drug cost/patient/course

- 6.36 \$ [redacted] per 24-week treatment course (\$ [redacted] revised during the evaluation to account for the Revised Arrangements for the Efficient Funding of Chemotherapy (EFC) Drugs, effective July 2013). This is compared to \$22,174 per 24-week bevacizumab treatment course (\$22,363 revised during the evaluation).

Estimated PBS usage and financial implications

- 6.37 This re-submission was not considered by DUSC.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (in bev + FOLFOX market)	[redacted] %	[redacted] %	[redacted] %	[redacted] %	[redacted] %
Market share (in FOLFOX market)	[redacted] %	[redacted] %	[redacted] %	[redacted] %	[redacted] %
Scripts ^a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to PBS (revised)	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to MBS	-	-	-	-	-
Net cost to MBS (revised)	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Estimated total net cost					
Submission's estimate	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Revised estimates	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

^a Assuming 12 scripts per treatment course, as estimated by the re-submission. Bev=bevacizumab
Source: Table 8 of the commentary.

- 6.38 Revised estimates have been incorporated into the table above. The net cost/year for the PBS may be greater than estimated in the re-submission given that:

- both the eligible population and the uptake of panitumumab are underestimated;
- the cost offset of later-line anti-EGFR antibody use in patients treated with first-line panitumumab is overestimated - it is not reasonable to assume that all patients will receive two or more lines of active treatment and that the market share held by anti-EGFR antibodies in the later-line setting (of RAS WT) is [redacted] %;
- an increase in PFS to between 11 and 13 months with the addition of panitumumab would be expected to increase the duration of therapy from the 12 cycles assumed (24 weeks or 6 months) and thus also increase the use of corresponding chemotherapy; and
- a significantly smaller increase in PFS of 9.5 months with the addition of bevacizumab from the 12 cycles assumed (24 weeks or 6 months) would be expected to increase the offsetting use of corresponding chemotherapy to a lesser extent.

- 6.39 Increased costs to the MBS for RAS testing over KRAS testing and for any earlier testing with the first-line listing of panitumumab are being considered by MSAC.

- 6.40 The proposed price of panitumumab in the first-line is the same as that agreed for later-line listing for which a special pricing arrangement is in place.

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

7 PBAC Outcome

- 7.1 The PBAC recommended that the current PBS restriction for panitumumab be amended urgently to include only patients with *RAS* WT mCRC. Based on the evidence provided for both PBS-listed anti-EGFR antibodies, the TGA amendments to the relevant product information documents, updated guidelines and the hearing, the PBAC advised that the inferior treatment effect for *RAS* mutant patients is a class-wide effect and so recommended that the current PBS restriction for cetuximab be amended in the same way at the same time. The PBAC also recommended that these amendments should be coordinated with corresponding amendments to the related MBS item descriptor to extend mutation testing to cover all *RAS* mutations, which is the subject of a coordinated submission to MSAC. As foreshadowed by the PBAC and MSAC in November 2013, the need for urgency arises because the evidence indicates that continuing the current restrictions based on identifying *KRAS* wild-type patients is predictably exposing some of these patients to worse health outcomes.
- 7.2 The PBAC rejected the request to amend the current PBS restriction for panitumumab to include first-line treatment of patients with *RAS* WT mCRC based on the uncertainty of the extent of incremental clinical benefit over its comparators.
- 7.3 In particular, the PBAC did not consider that it could rely on the median absolute overall survival of 41 months of panitumumab + FOLFOX and median gain in overall survival of 12.4 months over bevacizumab + FOLFOX alone in the *RAS* WT subgroup of the PEAK trial. These results are inconsistent with a median gain in PFS of 2.9 months in the same trial and data on equivalence of panitumumab and cetuximab. The results are also inconsistent with the absolute overall survival of both anti-EGFR antibodies + FOLFOX in other first-line trials, including the PRIME trial (median overall survival of 25.8 months for panitumumab + FOLFOX). Taken together the PBAC considered that the inconsistency of the OS results for panitumumab + FOLFOX in PEAK compared with the other studies meant these results could not be relied upon to quantify the benefit of panitumumab + FOLFOX compared to bevacizumab + FOLFOX.
- 7.4 The PBAC noted that the most recent systematic review of the two anti-EGFR antibodies in the first-line treatment of mCRC (Zhou et al, PLoS ONE 7(11), November 2012) found no survival benefit over oxaliplatin-based chemotherapy, but was based on the *KRAS* WT subgroup rather than the *RAS* WT subgroup. The PBAC therefore requested that a similar systematic review be conducted of all relevant trials with *RAS* WT results across both panitumumab and cetuximab in order to assess the totality of data for overall effect size. The PBAC noted that the CALBG/SWOG 80405 comparison of cetuximab with bevacizumab (with FOLFOX or FOLFIRI as chemotherapy partners) would be particularly relevant for inclusion in this meta-analysis because of its larger size than the PEAK trial. It would be most informative to present this analysis for the subgroup of patients with *RAS* WT (rather than only *KRAS* exon 2 WT).
- 7.5 This systematic review involving the *RAS* WT subgroup should present pooled estimates of treatment effect for at least PFS and OS, and should present these separately for the comparison of anti-EGFR antibody + chemotherapy versus chemotherapy alone and for the comparison of anti-EGFR antibody + chemotherapy versus bevacizumab + chemotherapy. In relation to these comparisons, the PBAC noted that there was no clear evidence that *RAS* mutation status predicted any treatment effect variation with either chemotherapy alone or bevacizumab + chemotherapy, so interpretation of the meta-analyses should not be biased against these comparator arms in relation to variation in their results across the subgroup analyses.

- 7.6 The PBAC advised that the systematic review should also consider the risks of bias and exchangeability issues highlighted by the ESC. In addition, the PBAC considered that the Zhou et al meta-analysis raises questions over whether the extent of incremental benefit of anti-EGFR antibodies varies with the choice of chemotherapy partner, with oxaliplatin-based chemotherapy being considered to be the least attractive partner. Similarly, bevacizumab is considered to be more effective when used with capecitabine, fluorouracil or FOLFIRI and least effective when used with oxaliplatin. Further investigation or comments on the impact of oxaliplatin partner chemotherapy would be informative. This investigation would helpfully be put into context by information on what proportions of current anti-EGFR antibody and current bevacizumab prescribing in mCRC is partnered with the different options. The impression of the PBAC was that oxaliplatin was the most frequently chosen partner chemotherapy.
- 7.7 The addition of panitumumab to FOLFOX appears to have an inferior safety profile compared to either bevacizumab + FOLFOX or FOLFOX alone.
- 7.8 The PBAC considered these comparators to be appropriate.
- 7.9 The PBAC generally considered the structure of the economic model to be acceptable, but considered that the following inputs require adjustment in order for the model to be reliable:
- Hazard ratios: these should be based on the results of the systematic review rather than the individual trials. In particular, the PBAC rejected the application of the favourable hazard ratios from the PEAK trial to the survival results of the panitumumab + FOLFOX arm from the PRIME trial as the basis of the comparison with bevacizumab + FOLFOX. The PBAC noted the ESC suggestion that it may be possible to base the consideration of first-line listing only on the PRIME-based comparison with FOLFOX alone given the PRIME trial is larger and produces less confounded results, but considered it more appropriate to await the results of the requested systematic review of this comparison to ascertain appropriate hazard ratios;
 - Post-progression costs: the PBAC considered that post-progression costs were inappropriately estimated in the model and accepted the ESC's basis for respecifying the base case of the model to reflect more appropriately the extent of post-progression use of anti-EGFR antibodies and bevacizumab after first-line therapy both in the trials and also expected in Australian practice. The PBAC also agreed that costs following progression after second-line therapy were underestimated (which favoured panitumumab), and noted that the increased the BSC per cycle cost of \$████ in the PSCR was a preferable estimate than \$████ in the re-submission;
 - Bevacizumab costs: the PBAC noted that the modelled comparison with bevacizumab also favours panitumumab because it uses the published price of bevacizumab, whereas special pricing arrangements are known to apply to the PBS listing of bevacizumab; and
 - Aggregated analysis weighted by expected proportion of substitution (step 8): the results of the model for each comparison should be considered separately.
- 7.10 The PBAC noted that estimates of the number of RAS WT patients with mCRC across all lines of therapy were underestimated.
- 7.11 In particular, the treatment duration for both panitumumab and bevacizumab are assumed to be 12 cycles in the RAS WT subgroup. The median PFS observed with

panitumumab + FOLFOX was 11 and 13 months in the PRIME and PEAK trials respectively, while the median PFS observed with bevacizumab + FOLFOX was 9.5 months. As treatment is proposed to continue until disease progression, the assumption of no difference in treatment duration overestimates cost offsets.

- 7.12 The PBAC considered that a Risk Sharing Arrangement would be appropriate for anti-EGFR antibodies should they be recommended for first line therapy in the future.
- 7.13 The PBAC noted that the PBS subsidy of first-line anti-EGFR antibodies would initiate a re-consideration of the current inability to use PBS-subsidised bevacizumab in the later-line treatment of mCRC. As per the current bevacizumab restriction, patients who use anti-EGFR antibodies first-line and experience disease progression would not be able to receive PBS-subsidised bevacizumab and so would only be able to receive further treatment with chemotherapy alone in the later-line setting. For this reason, prescribers might be directed towards predominately using bevacizumab first-line in order to maximise treatment options. The PBAC foreshadowed its intention to recommend relaxing the bevacizumab restriction to allow its use in mCRC after a first-line anti-EGFR antibody (ie one course only for the PBS-subsidised treatment of mCRC in a patient), but not to vary the basis of the risk-share arrangements for bevacizumab as these changes should not be expected to increase the extent of bevacizumab prescribing. The PBAC invited feedback on this proposal.
- 7.14 Similarly, the PBAC noted the ESC advice and the Pre-PBAC response on whether the PBS subsidy of first-line anti-EGFR antibodies would raise the need to decide whether to subsidise multiple uses or sequential use of these medicines in mCRC after disease progression. The PBAC noted the advice of the clinician at the hearing that this would be preferable. The PBAC foreshadowed its intention to allow sequential use, but only in the context of reducing the average price of the anti-EGFR antibodies to recognise the expected reduction in the extent of their incremental benefit with each sequential use. The PBAC invited feedback on this proposal.
- 7.15 Further, the PBAC noted the ESC advice and the Pre-PBAC response on the variation across the proposed and existing PBS restrictions for both panitumumab and bevacizumab in mCRC in relation to ECOG or WHO performance status. The PBAC foreshadowed its intention to allow first-line anti-EGFR antibodies in patients with a WHO performance status of 2 or less (consistent with their current PBS restriction in second-line mCRC), but to retain the current PBS restriction for bevacizumab in mCRC to patients with a WHO performance status of 2 or less. The PBAC invited feedback on this proposal.
- 7.16 The PBAC noted that this resubmission is not eligible for an Independent Review because it had recommended one of the two requests of the re-submission.

Outcome:

Recommended

8 Recommended listing

- 8.1 Amend existing panitumumab listing as follows (recommended amendments in bold type face):

Name, Restriction, Manner of administration and form	Max Amt	No. of Rpts	Proprietary Name and Manufacturer	
PANITUMUMAB panitumumab 100 mg/5 mL injection, 1 x 5 mL vial	720 mg	5	Vectibix®	AN
panitumumab 400 mg/20 mL injection, 1 x 20 mL vial				

Severity:	Metastatic
Condition:	colorectal cancer
Treatment phase:	Initial treatment
Restriction:	Section 100 (Efficient Funding of Chemotherapy (EFC)) Private Hospital/Private Clinic Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	Patient must have <i>RAS</i> wild-type metastatic colorectal cancer AND Patient must have a WHO performance status of 2 or less AND The condition must have failed to respond to first-line chemotherapy AND The treatment must be as monotherapy; OR The treatment must be in combination with an irinotecan based therapy AND The treatment must be the sole PBS-subsidised anti-EGFR antibody therapy for this condition.
Prescriber Instructions	Patients who have progressive disease on cetuximab are not eligible to receive PBS-subsidised panitumumab. Patients who have developed intolerance to cetuximab of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised panitumumab.
Administrative advice	Note Special Pricing Arrangements apply. Note Panitumumab is not PBS-subsidised for use in combination with oxaliplatin-based therapies.

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:	Patient must have received an initial authority prescription for panitumumab for treatment of <i>RAS</i> wild-type metastatic colorectal cancer after failure of first-line

	<p>chemotherapy</p> <p>AND</p> <p>Patient must not have progressive disease</p> <p>AND</p> <p>The treatment must be as monotherapy; OR The treatment must be in combination with an irinotecan based therapy</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 cetuximab are not eligible to receive PBS-subsidised panitumumab.</p> <p>Patients who have developed intolerance to cetuximab of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised panitumumab.</p>
Administrative advice	<p>Note Special Pricing Arrangements apply.</p> <p>Note Panitumumab is not PBS-subsidised for use in combination with oxaliplatin-based therapies.</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

Amgen acknowledges the PBAC's positive recommendation for modifying the panitumumab (and cetuximab) PBS restrictions from WT KRAS to WT RAS in the later-line setting. Amgen is disappointed with the PBAC's decision not to recommend panitumumab in first-line WT RAS patients, but remains committed to working with the PBAC towards a listing as soon as possible.

Taking into account the totality of the evidence considered by the PBAC Amgen believes that, in WT RAS patients, the effectiveness of panitumumab is greater than previously accepted as clinically meaningful in this setting.

Amgen would also like to provide the following corrections and clarifications to the information provided in the above Public Summary Document:

- It is incorrectly stated that all RAS WT patients in the comparator arm of the model were assumed to incur the cost of an EGFR inhibitor at progression (Section 6.24, table). In Amgen's model only a subset of patients were assumed to go on to receive subsequent EGFR therapy.

- In a response to a question at the hearing, the clinician expressed a personal preference to have both these medicines [*panitumumab and cetuximab*] available to be used in sequence with each other for a minority of patients (Section 6.1). Amgen wishes to note that this was not part of the hearing presentation nor was it being sought as part of the submission. Evidence to support EGFR inhibitors used sequence is limited.
- The PSD also suggests a “trend to a greater superiority in the RAS WT subgroups of the panitumumab studies” (Section 6.6). Whilst PEAK is a phase 2 study and demonstrated only a statistically significant difference in PFS in the RAS WT population, the phase 3 PRIME study demonstrated superiority of panitumumab in both PFS and OS in RAS WT patients.