Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1363 – RAS (KRAS and NRAS) mutation testing for eligibility to access panitumumab

Applicant: **Amgen Australia Pty Ltd**

Date of MSAC consideration: **MSAC Meeting, 3 October 2014**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

This 'fit-for-purpose' submission-based assessment (SBA) to MSAC was to:

1. request changes to MBS item 73330, recently replaced by item 73338, (Kirsten rat sarcoma oncogene (*KRAS*) mutation testing for cetuximab and panitumumab) to accommodate expanded rat sarcoma oncogene (*RAS*) mutation testing for both first-line and second- or later-line treatment of metastatic colorectal cancer (mCRC) (including by addressing issues raised by the November 2013 MSAC meeting regarding (i) responses of international regulatory agencies to the emerging evidence around *RAS* testing, (ii) how and when Australian pathology laboratories could change their testing practices to accommodate *RAS* testing, and (iii) the most cost-effective way to cover the additional gene testing);
2. inform MSAC considerations of any implications on mutation testing of extending the PBS reimbursement of panitumumab to include patients in the first-line setting; and
3. seek *RAS (KRAS* and *NRAS)* mutation testing for eligibility for panitumumab treatment in previously untreated metastatic colorectal cancer patients.

Amgen lodged a concurrent resubmission to PBAC, scheduled for consideration at the July 2014 PBAC meeting, to:

1. request a modification of the existing second-line panitumumab PBS restriction for mCRC which would require eligible patients to have *RAS* [Kirsten (*K*)*RAS* + neuroblastoma (*N*)*RAS*] wild type (WT) tumours; and
2. request PBS listing for panitumumab in the first-line treatment of patients with mCRC and *RAS* WT tumours.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of testing to select eligible patients with colorectal cancer for panitumumab or cetuximab treatment, MSAC advised the Minister that the current MBS item descriptor for *KRAS* mutation testing (73338) be amended urgently to instead refer to *RAS* mutation testing and thus allow testing for additional *RAS* mutations.

MSAC advised the following item descriptor would be suitable:

> A test of tumour tissue from a patient with metastatic (stage IV) colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to ras sarcoma oncogene (*RAS*) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC advised that the costs for testing additional mutations should be recognised by increasing the MBS fee to $362.59.

Given the pace of technological improvements, MSAC recommended a review of the testing fee should occur in no less than 24 months to ensure efficient use of MBS benefits. Applications for additional somatic genetic testing for CRC should also trigger a review of the cost effectiveness of *RAS* testing. MSAC noted that that genetic testing would reach a point where gene panel testing (and possibly exome sequencing) would be clinically appropriate and more cost-effective than reimbursing testing on a gene by gene basis.

MSAC recommended that the Department notify the Royal College of Pathologists of Australasia (RCPA) quality assurance program (QAP) of the recommendation so that processes can be developed to ensure that extended *RAS* testing meets the same standards as for *KRAS* testing. Given the potential for harm associated with exposure of patients with *RAS* mutant tumours to anti-EGFR inhibitors it was considered particularly important to employ testing strategies which accurately exclude the presence of a *RAS* mutation.

MSAC advised that these changes should be coordinated with corresponding amendments to the relevant PBS restrictions for panitumumab and cetuximab.

MSAC further advised that, in the event that PBAC recommends that the PBS restriction of panitumumab or cetuximab should be extended to include the first-line treatment of metastatic colorectal cancer, this MBS item descriptor would not require any further amendment to allow for earlier testing.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that, given the risk of harm associated with exposing patients with *RAS* mutations to anti-EGFR inhibitors, the Department of Health convened an urgent executive MSAC meeting to consider this co-dependent application. The minutes of this meeting and the submission will be tabled at the full MSAC meeting in November 2014.

MSAC noted that, although the application referred to MBS items 73330 and 73338 as being relevant, MBS item 73330 is in the process of being phased out, and so confined its considerations to MBS item 73338.

MSAC found the evidence presented to constitute a compelling basis to extend the mutation testing of patients with metastatic colorectal cancer from *KRAS* (exon 2, codons 12/13) only to also allow testing for other *RAS* mutations. MSAC agreed with the July 2014 PBAC advice that, as foreshadowed by the PBAC and MSAC in November 2013, the clinical evidence indicates that continuing the current PBS restrictions for anti-EGFR antibodies based on only identifying *KRAS* wild-type patients is predictably exposing some of these patients to worse health outcomes. Expanding testing to include all *RAS* mutations and limiting subsidy of anti-EGFR antibodies to those patients demonstrated to have no *RAS* mutations both reduces harms and improves health outcomes.

MSAC agreed with the Evaluation Sub-Committee (ESC) that, based on the clinical evidence overall, the identified effect of *RAS* mutation status in predicting a reduced treatment effect is:

- operating as a class effect across anti-EGFR antibodies, i.e., it similarly affects both panitumumab and cetuximab
- consistent irrespective of the chemotherapy partner used with the anti-EGFR antibody
- found when anti-EGFR antibodies are used as monotherapy
- likely to be consistent across all lines of therapy **(redacted)**.

MSAC noted ESC's caveats with this evidence in relation to the lack of prespecification of the analysed sub-groups and absence of test for interaction, the inability to assess other potential confounders, and the fact that some of the subgroups were small. However MSAC considered that the strong biological plausibility and consistency of this effect across multiple studies was particularly persuasive.

MSAC also agreed with ESC that, although the effect is extended beyond mutations on *KRAS* exon 2 to include *KRAS* exons 3 and 4, and to *NRAS* exons 2, 3 and 4, other theoretically relevant mutations such as *BRAF* and *PIK3CA* mutations have not yet been proven to predict anti-EGFR antibody response. Further, MSAC was not able to determine that the associated assays for *BRAF* and *PIK3CA* mutations have been analytically validated.

MSAC noted advice from the application and ESC that the logistics for extended *RAS* mutation testing are essentially identical to *KRAS* mutation testing and that pathology laboratories are modifying their testing practices quickly.

MSAC agreed with ESC that an economic evaluation confined to the proposal for extended *RAS* mutation testing compared to current *KRAS* mutation testing would result in dominance for *RAS* mutation testing because this would reduce the proportion of existing patients receiving additional panitumumab resulting in inferior health outcomes, and the increased costs of *RAS* mutation testing would be outweighed by the decreased costs of panitumumab.

MSAC considered the most cost-effective way of implementing an extension of *RAS* mutation testing would be to allow pathology laboratories to determine the most efficient approach to testing multiple exons and to develop a simple single MBS item for expanded *RAS* mutation testing. MSAC noted it was important that the laboratories are capable of providing the complete suite of *RAS* mutation tests, and that testing be conducted for all known *RAS* exons until either a mutation is found or the full range of exons are tested. MSAC noted that there was less data on the performance characteristics of assays for testing *NRAS* than for *KRAS* and that some laboratories would need to develop in-house methods for *NRAS* testing. MSAC agreed that the RCPA QAP would play an important role in ensuring extended *RAS* testing met the exacting standards required for testing in this clinical context.

MSAC agreed that there was insufficient basis to modify the MBS item descriptor to specify the test methods or approach to testing (type of tumour tissue tested or whether all *RAS* exons are tested simultaneously or sequentially). MSAC considered it was unnecessary to specify the diagnostic sensitivity in the item descriptor, however the RCPA QAP program should ensure test strategies in Australia are designed to minimise the risk of exposure of patients with *RAS* mutant tumours to anti-EGFR inhibitors.

MSAC also agreed that a transition MBS item for limited retesting of patients who previously only received *KRAS* mutation testing would not be necessary as this would be a small and diminishing population. MSAC accepted that testing for more *RAS* mutations would result in additional costs (at least over the immediate term) and so accepted that it would be reasonable to increase the MBS fee accordingly. MSAC noted the various options from the application, the Pathology Services Advisory Committee (PSAC) and ESC for setting a single fee for expanded *RAS* mutation testing and advised that a fee of $362.59 had the strongest evidence base.

MSAC noted ESC's concerns with the application's financial estimates, and agreed that these overestimated the net cost to the MBS of expanding from *KRAS* mutation testing to *RAS* mutation testing. MSAC suggested that the indicative estimates from ESC would provide the Department with a better basis for estimating these financial implications.

In 2013, MSAC requested information be provided to inform an MSAC judgement of whether patients diagnosed with colorectal cancer, which is not metastatic, should also be tested so that the mutation status is already known at the time such patients may progress to metastatic disease. MSAC noted that the application requested that the tested population not be changed to coincide with the parallel request of PBAC to expand the PBS restriction to subsidise panitumumab as first-line therapy of metastatic colorectal patients

MSAC noted ESC advice that for a variety of reasons there is some discordance of *RAS* mutation status between primary and metastatic lesions. Wherever possible, current best clinical practice is to perform mutation testing on a metastatic rather than the primary colorectal cancer. Currently 8% of *KRAS* mutation tests are performed on non-metastatic colorectal cancer samples. Given the practicalities of obtaining metastatic tumour material for testing MSAC considered this figure was not unreasonable. The subsidy of anti-EGFR antibodies as first-line use in metastatic colorectal cancer should not be used as a rationale for substituting mutation testing on primary CRC tumours in place of testing metastatic lesions.

MSAC noted that the evidence presented in the current application also affirmed its previous recommendations (MSAC PSD 2011, p8) that *RAS* testing be eligible for reimbursement when the patient is diagnosed with metastatic disease. This view was also supported by the clinical experts who contributed to the application.

4. Background

In December 2010, MSAC supported public funding of testing to determine *KRAS* mutation status of tumour material from patients with mCRC to contribute to the determination of eligibility for PBS-subsidised second line cetuximab treatment. Testing was suggested to be performed in a National Association of Testing Authorities (NATA) accredited laboratory, and to be ordered by an oncologist. It was also recommended that testing be supported by suitable quality standards and a quality assurance program (QAP) specific to *KRAS* mutation testing developed by the Royal College of Pathologists of Australasia (RCPA). This advice was implemented on 1 May 2011 with the creation of MBS Item 73330.

In April 2013, MSAC supported the extension of the current MBS item for *KRAS* mutation testing to include panitumumab, as well as cetuximab, when testing tumour tissue from a patient with mCRC in order to determine if the requirements for access to these treatments under the PBS are fulfilled. On 1 April 2014, MBS Item 73338 was implemented to determine eligibility for access to either cetuximab or panitumumab.

In November 2013, MSAC considered issues surrounding expanded *RAS* (and other) mutation testing under MBS item 73330 for access to cetuximab/panitumumab. Some of these issues had been raised by PBAC during its consideration of panitumumab as second-line therapy at its November 2013 meeting. In particular, emerging evidence suggested that patients with *KRAS* exon 2 WT but other *RAS* mutations experienced poorer treatment outcomes when treated with panitumumab or cetuximab in combination with chemotherapy compared with chemotherapy alone. MSAC highlighted that maintaining the status quo of only *KRAS* exon 2 testing will result in a subset of patients being unnecessarily exposed to side effects and reduced treatment outcomes with cetuximab/panitumumab. MSAC sought further information from the sponsors, Amgen and Merck Serono, and from the TGA on matters related to re-defining the appropriate biomarker testing in metastatic colorectal cancer to guide treatment with cetuximab and panitumumab (that was to be assessed via MSAC ESC).

5. Prerequisites to implementation of any funding advice

No specific test has been requested for the MBS listing. Most *RAS* mutation testing is likely to be under the control of an Approved Pathology Authority, such as NATA, and therefore must meet the requirements for TGA registration.

6. Proposal for public funding

The SBA assumed that MBS Items 73330 (and 73338) can cover testing of both *KRAS* exons 2 and 3. MSAC noted that the SBA presented five different scenarios for the additional testing of *KRAS* exon 4 and *NRAS* exons 2, 3 and 4 to determine eligibility for treatment with panitumumab or cetuximab. The critique noted that testing for *KRAS* exon 4 mutations could be considered to be already covered under the current wording of these MBS items.

In two scenarios presented in the SBA, the additional testing would be listed under a new MBS item number, with the current MBS Item 73338 (reflecting the addition of 'and panitumumab', as of 1 April 2014) remaining unchanged. The wording of the new item would depend on the sequence and timing of the additional testing:

- new Item A (scenario A) involves cascade testing of patients with *KRAS* exon 2 and 3 WT mutation status; or
- new Item B (scenario B) would allow concurrent or cascade testing of all *KRAS* and *NRAS* exons as required.

Applicant proposed new MBS item descriptor for *RAS* mutation testing of additional *KRAS*/*NRAS* exons

Category 6 – Pathology Services Group P7 - Genetics
New Item A A test of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if a patient previously confirmed as KRAS wild type under Item 73330 [sic] meets the requirements relating to RAS (Kirsten ras (KRAS) and neuroblastoma ras (NRAS)) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Fee: $296.00
New Item B This service may be provided in conjunction with Item 73330 [sic]. A test of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to RAS (Kirsten ras (KRAS) and neuroblastoma ras (NRAS)) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $296.00

The critique suggested rewording the proposed descriptors to improve readability of the item descriptors and acknowledge that a patient is already known to be *KRAS* wild type.

Suggested rewording of the proposed MBS item descriptor for *RAS* mutation testing of additional *KRAS*/*NRAS* exons

Category 6 – Pathology Services *Group P7 - Genetics*
New Item A *A test of tumour tissue, from a patient with metastatic colorectal cancer previously confirmed as KRAS wild type under Item 73338, requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to neuroblastoma ras (NRAS) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.* *Fee:*
New Item B *This service may be provided in conjunction with Item 73338. A test of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to neuroblastoma ras (NRAS) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.* *Fee:*

The SBA presented two additional scenarios which involve changing the wording of MBS item number 73338 to reflect scenarios allowing for testing of all *RAS* mutations either simultaneously or concurrently with the fee based on:

- the total cost of testing all *KRAS* and *NRAS* exons, regardless of laboratory practices with regard to cascade testing ($534.00; scenario C); or
- an average weighted cost based on cascade testing of samples with the fee determined by the proportion of samples requiring *KRAS* exon 2 and 3 testing only ($399.67; scenario D).

The fifth scenario presented in the SBA recognised that changing the wording of MBS item number 73338 may require a temporary new item for patients already assessed for *KRAS* exon 2 mutations (and possibly exon 3 mutations). The SBA proposed that the fee for this "bridging code" be set at $296.00 (scenario E) which would apply in addition to the existing KRAS fee of $230.95. The critique noted that with the suggested wording for items A and B above, this bridging item would not be required.

Applicant proposed new MBS item descriptor for *RAS* mutation testing of all *KRAS*/*NRAS* exons

Category 6 – Pathology Services Group P7 - Genetics
New Item C or D A test of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if patient meets the requirements relating to RAS (Kirsten ras (KRAS) and neuroblastoma ras (NRAS)) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $534.00 (C) or $399.67 (D)
Temporary new item A test of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if patient previously confirmed as WT KRAS under Item 73330 [sic] meets the requirements relating to RAS (Kirsten ras (KRAS) and neuroblastoma ras (NRAS)) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $296.00

7. Summary of Public Consultation Feedback/Consumer Issues

Submissions received from the public noted the current limited access to expanded *RAS* mutation testing, because only 40% of laboratories have made this expansion as at August 2013. If expanded *RAS* mutation testing is likely to increase the possibility of a patient having to return to provide an extra sample of tumour tissue, this would have consequences for the patient beyond any harms from obtaining the sample, including the time and travel costs required to return.

Comments from the public reflected awareness of the consequences of expanded *RAS* mutation testing for subsequent treatment decisions to optimise health outcomes and reduce treatment costs by minimising the suboptimal use of panitumumab and cetuximab.

Consumers noted the complex terminology involved, which is a source of confusion when patients try to understand the impact of testing on their prognosis by improving the management of their disease – and whether they choose one intervention over another, or over no medical intervention, at a given time.

Increases in out-of-pocket payments charged to patients are thought likely.

8. Proposed intervention's place in clinical management

The proposed medical service is a genetic pathology test aimed at detecting somatic *RAS* mutations in CRC tumour tissue.

The SBA proposed that expanded *RAS* mutation testing will replace the current *KRAS* mutation testing funded under MBS item numbers 73330 and 73338. Testing of the additional exons will occur either concurrently, or as cascade testing of samples (i.e., only samples that do not have *KRAS* mutations will be tested for *NRAS* mutations).

Currently, MBS Item 73338 provides for *KRAS* mutation testing of tumour material from patients with mCRC to assess eligibility for cetuximab or panitumumab according to the requirements of the PBS. The evidence base for this item primarily related to the detection of *KRAS* exon 2 mutations, but the wording of the item could be considered to allow for the

detection of mutations in *KRAS* exons 3 and 4. However, the current item does not include the detection of *NRAS* exon 2, 3 and 4 mutations, or any other rarer *RAS* mutation.

The *RAS* mutation test, as currently commonly performed, will need to expand from sequencing *KRAS* exon 2 (codons 12/13), exon 3 (codons 59/61), and exon 4 (codons 117/146) to introduce testing for *NRAS* exon 2 (codons 12/13), exon 3 (codons 59/61) and exon 4 (codons 117/146), and possibly for *HRAS*.

From the 2011 EMA Assessment Report for panitumumab, the prevalence of these 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%).

The SBA proposed that the place of *RAS* mutation testing in clinical management would be identical to the current place of *KRAS* mutation testing: i.e., upon diagnosis of metastatic disease, prior to commencement of treatment with anti-EGFR antibodies.

The other possible extension of testing for MSAC to consider was whether to drop the current requirement that a patient have the metastatic stage of CRC before being eligible for MBS-subsidised testing. The SBA proposed retention of the current requirement to mCRC.

9. Comparator

The proposed testing pathway is identical to the current pathway, except that *RAS* mutation testing extends beyond current *KRAS* mutation testing, which occurs at diagnosis of mCRC. The only difference between the proposed and current clinical management pathways is the proposed timing of panitumumab therapy (first-line versus second-line).

As there is currently no public funding for *NRAS* (or *HRAS*) mutation testing in any setting, the comparator for *RAS* mutation testing is *KRAS* mutation testing alone. This is considered appropriate.

The MBS items for the comparator, *KRAS* mutation testing, are:

Category 6 – Pathology Services Group P7 - Genetics
73330 A test of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to Kirsten ras (KRAS) gene mutation status for access to cetuximab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $230.95; Benefit: 75% = $173.25, 85% = $196.35
73338 A test of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to Kirsten ras (KRAS) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $230.95; Benefit: 75% = $173.25, 85% = $196.35

10. Comparative safety

At its December 2010 meeting, MSAC agreed that the *KRAS* mutation testing is safe for patients as it uses a sample already collected for histological assessment from patients diagnosed with mCRC. This will not change with *RAS* mutation testing, which is performed using the same approach.

Expanded testing, particularly where testing is done serially (such as where a patient's tumour has previously been tested for *KRAS* mutations) may require additional material for testing, which would usually be obtained from stored tumour tissue rather than from a new sample.

The SBA stated that any *RAS* mutation testing that is to be funded must be performed in a NATA-accredited laboratory, which is demonstrated via a suitable RCPA-ratified QAP to be proficient in the technique employed. The SBA also stated that there is currently no RCPA QAP for *NRAS* mutation testing, however, NATA accreditation only requires that each laboratory must maintain quality systems that should provide laboratory management with continuing confidence that results and conclusions are accurate and reliable. Advice from PSAC indicated that development of an RCPA QAP for *NRAS* mutation testing is underway, and will be similar to that already in place for *KRAS* mutation testing.

11. Comparative effectiveness

Almost half the laboratories participating in the RCPA QAP use DNA sequencing, and all demonstrate a high level of concordance (98.7%) regardless of method used, suggesting that the number of patients receiving a false negative or false positive result will be small. It is possible, however, that detection limitations in current methodologies may lead to a higher false negative rate than currently estimated. *KRAS* mutation testing has been accepted by MSAC as satisfactorily adequate, and while *RAS* mutation testing is not widely conducted in Australia at this point, the technology, and therefore the factors affecting accuracy, will be identical.

Extending *KRAS* mutation testing to *RAS* mutation testing

Retrospective analyses comparing PFS and OS outcomes in patients with *KRAS* exon 2 WT, *RAS* WT or *RAS* mutation-positive (M+) tumours found that hazard ratios for *RAS* WT patients favoured treatment with anti-EGFR antibodies (i.e., panitumumab or cetuximab) in 7/7 trials for PFS and 6/8 trials for OS. The difference in median PFS (5/6 trials) and OS (6/7 trials) comparing the anti-EGFR antibody (plus chemotherapy) treatment arm to the chemotherapy alone arm was greater in patients with *RAS* WT tumours compared to patients with *KRAS* exon 2 WT tumours. The *RAS* M+ subgroup had a worse prognosis when treated with anti-EGFR antibodies ± chemotherapy compared to chemotherapy alone in 6/7 trials for PFS and 5/8 trials for OS. However, statistical significance was not achieved in most trials (likely due to lack of power).

The validity of the results could not be reliably assessed for three of the eight included trials and potential confounders could not be ruled out for five of these. Clinical evidence for cetuximab presented in Amgen's SBA (and hence, what was critiqued) was limited to information in the public domain, as the manufacturer of cetuximab (Merck Serono) had not lodged submissions with PBAC or MSAC at the time of evaluation. The impact of *RAS* mutations on treatment outcomes was consistent across lines of therapy and background chemotherapy for panitumumab. For cetuximab, the results for treatment effect in *RAS* M+ patients have only been reported for the first-line setting. Overall, the results suggest that anti-EGFR antibody ± chemotherapy treatment in *RAS* M+ patients may be detrimental to survival outcomes.

Patients with low levels of *KRAS* M+ cells had a worse prognosis for PFS (3/3 studies) and response rate (3/4 studies) compared to those with *KRAS* WT tumours after anti-EGFR antibody treatment ± chemotherapy. However, due to a lack of data for the comparator arm, the presence of a prognostic effect from *RAS* mutation status could not be assessed. No

prognostic effect was associated with PFS in chemotherapy patients with *RAS* WT tumours compared to those with *KRAS* exon 2 WT/*RAS* M+ tumours.

OS and PFS results are summarised in the tables below.

Summary of PFS comparing treatment with anti-EGFR antibodies plus chemotherapy or best supportive care compared to chemotherapy or best supportive care alone

Study	*KRAS* exon 2 WT population		*RAS* WT population (*KRAS*/*NRAS* exons 2/3/4)		*KRAS* exon 2 WT, *RAS* M+ population	
First line treatment	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator
PRIME n	325	331	259	253	51	57
median PFS (months)	9.6	8.0	10.1	7.9	7.3	8.0
Difference in PFS	*+1.6*		*+2.3*		*-0.7*	
HR (95% CI)	0.80 (0.66, 0.97)		0.72 (0.58, 0.90)		1.28 (0.79, 2.07)	
Number of events			156 (60%)	170 (67%)	38 (75%)	35 (61%)
HR (95% CI)			0.722 (0.579, 0.901)		1.276 (0.786, 2.071)	
Quantitative Interaction Test			p = 0.0361			
PEAK n	142	143	88	82	24	27
median PFS (months)	10.9	10.1	13.0	9.5	7.8	8.9
Difference in PFS	*+0.8*		*+3.5*		*-1.1*	
HR [95% CI]	0.87 (0.65, 1.17)		0.65 (0.44, 0.96)		1.39 (0.73, 2.64)	
Number of events			50 (57%)	60 (73%)	21 (88%)	18 (67%)
HR (95% CI)			0.651 (0.444, 0.956)		1.387 (0.730, 2.635)	
Quantitative Interaction Test			p = (redacted)			
	Cmab	Comparator	Cmab	Comparator	Cmab	Comparator
FIRE-3 n	297	295	171	171	65	
median PFS (months)	10.0	10.3	10.4	10.2	6.1	12.2
Difference in PFS	*-0.3*		*+0.2*		*-6.1*	
HR (95% CI)	1.06 (0.88, 1.26)		0.93 (0.74, 1.17)		2.22 (1.28, 3.86)	
OPUS n	82	97	36	46	17	19
median PFS (months)	8.3	7.2	12.0	5.8	7.3	7.4
Difference in PFS	+1.1		+6.2		-0.1	
HR (95% CI)	0.57 (0.38, 0.86)		0.43 (0.21, 0.88)		1.02 (0.41, 2.55)	
Later-line treatment	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator
Study 181 n	303	294	107		107	
median PFS (months)	5.9	3.9	6.4	4.4	(redacted)	(redacted)
Difference in PFS	*+2.0*		*+2.0*		(redacted)	
HR (95% CI)	0.73 (0.59, 0.90)		0.695 (0.536, 0.903)		0.892 (0.561, 1.419)	
Study 408 n	124	119	*72*	*61*	*11*	*11*
median PFS (weeks)	12.3	7.3	*12.3*	*6.9*	(redacted)	(redacted)
Difference in PFS	*+5.0*		*+5.4*		(redacted)	
HR [95% CI]	0.45 (0.34, 0.59)		*0.38 (0.27, 0.56)*		*0.81 (0.29, 2.26)*[a]	
Number of events			NR	NR	NR	NR
HR (95% CI)			0.39 (0.27, 0.56)		1.94 (0.44, 8.44)[b]	
Quantitative Interaction Test			(*KRAS* exon 2/3 WT, *NRAS* WT) (*KRAS* exon 2/3 WT, *NRAS* M+) p = (redacted)			
PICCOLO	*(KRAS exon 2/3 WT)*		*(KRAS/NRAS/BRAF/PIK3CA WT)*		*(Any mutant)*	
PFS n	*230*	*230*	*160*	*163*		
number of events/n			*276/323*		*123/137*	
HR (95% CI)	*0.78 (0.64, 0.95)*		*0.68 (0.53, 0.86)*		*1.20 (0.83, 1.74)*	

[a] As reported in the EMA Assessment report for panitumumab (June 2013). Note the small sample sizes and likely lack of statistical power for the comparison.

[b] As reported in Table 4.1-9 in the SBA

Comparator: PRIME = FOLFOX, PEAK = bevacizumab + FOLFOX, FIRE-3 = bevacizumab + FOLFIRI, OPUS = FOLFOX, Study 181 = FOLFIRI, Study 408 = best supportive care, PICCOLO = irinotecan; Cmab = cetuximab plus chemotherapy (same as comparator); Pmab = panitumumab plus either chemotherapy (same as comparator in PRIME, PEAK, Study 181 and PICCOLO) or best supportive care (Study 408).

Source: Tables 4.1-2, 4, 6, 8, 9-13 of the SBA; Peeters et al (2013); Seymour et al (2013), *EMA Assessment report for panitumumab (June 2013)*

Summary of OS comparing treatment with anti-EGFR antibodies plus chemotherapy or best supportive care compared to chemotherapy or best supportive care alone

Study	*KRAS* exon 2 WT population		*RAS* WT population (*KRAS*/*NRAS* exons 2/3/4)		*KRAS* exon 2 WT, *RAS* M+ population	
First line treatment	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator
PRIME n	325	331	259	253	51	57
median OS (months)	23.9	19.7	25.8	20.2	17.1	17.8
Difference in OS	*+4.2*		*+5.6*		*-0.7*	
HR (95% CI)	0.83 (0.67, 1.02)		0.77 (0.64, 0.94)		1.39 (0.91, 2.13)	
Number of events			204 (79%)	218 (86%)	46 (90%)	46 (81%)
HR (95% CI)			0.772 (0.637, 0.937)		1.394 (0.914, 2.127)	
Quantitative Interaction Test			p = 0.0126			
PEAK n	142	143	88	82	24	27
median OS (months)	34.2	24.3	41.3	28.9	27.0	16.6
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)	
Number of events			30 (34%)	40 (39%)	10 (42%)	21 (78%)
HR (95% CI)			0.625 (0.385, 1.016)		0.407 (0.191, 0.869)	
Quantitative Interaction Test			p = (redacted)			
	Cmab	Comparator	Cmab	Comparator	Cmab	Comparator
FIRE-3 n	297	295	171	171	65	
median OS (months)	28.7	25.0	33.1	25.6	16.4	20.6
Difference in OS	*+3.7*		*+7.5*		*-4.2*	
HR (95% CI)	0.77 (0.62, 0.96)		0.70 (0.53, 0.92)		1.20 (0.64, 2.28)	
OPUS n	82	97	36	46	17	19
median OS (months)	22.8	18.5	20.7	17.8	14.8	17.8
Difference in OS	*+4.3*		*+2.9*		*-3.0*	
HR (95% CI)	0.86 (0.60, 1.22)		0.83 (0.49, 1.41)		1.41 (0.62, 3.21)	
COIN	*(KRAS exon 2/3 WT)*		*(KRAS/NRAS exon 2/3 BRAF WT)*		*(any KRAS/NRAS/BRAF M+)*	
n	*362*	*367*	*292*	*289*	*366*	*340*
median OS (months)	*17.0*	*17.9*	*19.9*	*20.1*	*12.7*	*14.4*
Difference in OS	*-0.9*		*-0.2*		*-1.7*	
HR (95% CI)	*1.04 (0.87, 1.23)*		*1.02 (0.83, 1.24)*		*1.00 (0.85, 1.18)*	
Later-line treatment	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator
Study 181 n	303	294	107		107	
median OS (months)	14.5	12.5	16.2	13.9	11.3	9.2
Difference in OS	*+2.0*		*+2.3*		*-2.1*	
HR (95% CI)	0.85 (0.70, 1.04)		0.803 (0.629, 1.024)		1.39 (0.91, 2.13)	
Study 408 n	*124*	*119*	*72*	*61*	*11*	*11*
median OS (months)	*8.1*	*7.6*	*8.1*	*7.5*	*6.2*	*5.2*
Difference in OS	*+0.5*		*+0.6*		*+1.0*	
HR [95% CI]	*0.99 (0.75, 1.30)*		*1.03 (0.71, 1.48)*		*0.96 (0.37, 2.51)*[a]	
PICCOLO	*(KRAS exon 2/3 WT)*		*(KRAS/NRAS/BRAF/PIK3CA WT)*		*(Any mutant)*	
OS n	*230*	*230*	*160*	*163*		
number of events/n			*286/323*		*133/137*	
HR (95% CI)	*1.01 (0.83, 1.23*		*0.92 (0.73, 1.16)*		*1.64 (1.14, 2.34)*	

a Note the small sample sizes and likely lack of statistical power for the comparison.

Comparator: PRIME = FOLFOX, PEAK = bevacizumab + FOLFOX, FIRE-3 = bevacizumab + FOLFIRI, OPUS = FOLFOX, COIN = oxaliplatin and fluoropyrimidine chemotherapy, Study 181 = FOLFIRI, Study 408 = best supportive care, PICCOLO = irinotecan; Cmab = cetuximab plus chemotherapy (same as comparator); Pmab = panitumumab plus chemotherapy (same as comparator in PRIME, PEAK, Study 181 and PICCOLO) or best supportive care (Study 408).

Source: Tables 4.1-3, 5, 7, 8, 11-13 of the SBA; Maughan et al. (2011); Peeters et al (2013); Seymour et al (2013), *EMA Assessment report for panitumumab (June 2013).*

Consequences for testing of extending to include first-line panitumumab

While it is expected that each patient would only be tested once, there is uncertainty surrounding discordant *RAS* mutation status between primary and metastatic tumours. This extends to retrieving stored samples for patients who later progress to metastatic disease.

In addition, as noted previously by MSAC and currently in the critique, there is a theoretical risk of earlier testing (i.e., pre mCRC) if panitumumab or cetuximab become available on the PBS for first line mCRC treatment (that is, to allow sufficient time for testing prior to treatment commencement).

As noted in the critique, currently 8% of *KRAS* mutation tests are performed on non-metastatic tissue. The critique notes that MSAC may wish to consider specifying the source of tumour tissue as metastatic. However, ESC noted that there would likely be reasonable clinical grounds for using pre-metastatic tissue in situations where metastatic samples cannot be obtained (e.g., due to location, vascularisation).

12. Economic evaluation

No economic evaluation was presented in the SBA to MSAC, but findings from the applicant's submission to the July 2014 PBAC meeting were quoted in the SBA. The SBA was limited to a discussion of the proposed MBS fee(s) for *RAS* mutation testing.

Extended *RAS* mutation testing will necessitate designing, optimizing, validating and running another 4 or 5 primer pairs per sample for a total of 6 amplicons (*KRAS* exon 2/3/4 and *NRAS* exons 2/3/4).

The SBA stated that the current MBS reimbursement ($230.95) for *KRAS* (73330) was based on the cost of analysing amplicons generated by one pair of primers for exon 2. Several laboratories are currently conducting analysis of both exon 2 and 3 under Item code 73330, suggesting that it is sufficient for patient assessment to that extent. The cost of including another 4 amplicons for *KRAS* exon 4 and *NRAS* exons 2/3/4 will vary depending upon the method employed by the individual laboratories and whether the expanded *RAS* mutation test will be performed sequentially or concurrently.

The exact fee for *RAS* mutation testing will depend on the scenario MSAC deems appropriate. For cascade testing, the fee for *RAS* mutation testing will be unchanged at $230.95 for patients with *KRAS* exon 2/3 mutations with an additional $296.00 for those who are *KRAS* exon 2/3 WT to test for the additional *RAS* biomarkers. For concurrent testing of all *KRAS*/*NRAS* mutations, the fee would be $534.00. If both cascade and concurrent testing are considered appropriate, the fee would either reflect actual usage of *KRAS* exon 2/3 testing ($230.95) and *RAS* cascade testing of *KRAS* exon 2/3 WT ($296.00) if two MBS items are listed, or a weighted average of $399.67, if only one MBS item is listed (see Section 4 for a detailed description of the various testing scenarios and the associated proposed fee).

The expansion of testing from *KRAS* to *RAS* was assumed to lead to:

- an increase in the cost of testing (including the need to re-test a proportion of patients with previously identified *KRAS* WT status);
- a decrease in later-line anti-EGFR antibody treatment costs, as some patients will no longer be eligible for anti-EGFR antibody treatment; and
- improved patient outcomes compared with current practice (on the basis of data presented in Section 4.1 of the SBA).

The SBA concluded that the decrease in anti-EGFR antibody treatment costs will outweigh the increased cost of testing, and so overall there will be net cost savings to the government from this proposed restriction change. Given the net cost savings and the expected improvement in patient outcomes, the SBA concluded that the expansion of testing from *KRAS* to *RAS* is economically dominant. However, ESC noted that this conclusion was based on modelling which assumed that the applicant's request for a first-line mCRC listing for panitumumab was successful. In its pre-MSAC response, the applicant re-emphasised the rationale for its position, that the case for dominance with the introduction of *RAS* in the later-line setting is independent of consideration of or any modelling to support the proposed first-line listing.

13. Financial/budgetary impacts

The five scenarios for MBS listing of *RAS* mutation testing identified above are each associated with a different cost to the MBS (see table below). The incident cases of mCRC per year were based on estimates previously presented to the PBAC. To estimate the proportion of patients that undergo re-testing for *RAS* mutation status, the SBA assumed that 57% of incident cases previously had *KRAS* WT status; of these, it is assumed that, in the first year, 50% may still be eligible for anti-EGFR antibody treatment.

Regardless of the *RAS* mutation testing scenario, the same numbers of patients are assumed to be identified as eligible for anti-EGFR antibody treatment. The SBA did not attempt to quantify any other benefits associated with concurrent testing, and so the most efficient testing scenario, on the basis of cost-minimisation, would be the cheapest one proposed (scenario A, in which *RAS* mutation testing is conditional upon an earlier *KRAS* exon 2, 3 WT conclusion).

Estimated cost to the MBS for the five suggested *RAS* mutation testing scenarios

	Testing scenario descriptor	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year cost
Base number of patients to be tested[a]	-	6046	*6218*	*6391*	*6567*	*6747*	-
Number of patients previously deemed as *KRAS* WT (predominantly exon 2 & 3)	-	*3446*	*3544*	*3643*	*3743*	*3846*	-
Estimated proportion of *KRAS* WT patients requiring retesting	-	50%	25%	-	-	-	-
Total cost scenario A	Proposed new item allows cascade testing of patients with *KRAS* exon 2 and 3 WT mutation status	$2,926,228	*$2,747,247*	*$2,554,471*	*$2,624,453*	*$2,696,713*	*$13,549,111*
Total cost scenario B[b]	Proposed new item allows concurrent or cascade testing of all *KRAS* and *NRAS* exons as required	$3,695,705	*$3,538,623*	*$3,367,975*	*$3,460,244*	*$3,555,516*	*$17,618,062*
Total cost scenario C	Proposed item replaces current item, and assumes concurrent testing of all patients (full fee of *KRAS* and *RAS* mutation testing)	$4,148,396	*$3,793,327*	*$3,413,034*	*$3,506,538*	*$3,603,085*	*$18,464,380*
Total cost scenario D	Proposed item replaces current item, and assumes concurrent testing of all patients (weighted fee of *KRAS* and *RAS* mutation testing)	$3,104,849	*$2,839,099*	*$2,554,471*	*$2,624,453*	*$2,696,713*	*$13,819,585*
Total cost scenario E	As for C, however proposes a temporary item for patients previously assessed for *KRAS* mutation status	$3,738,326	*$3,582,457*	*$3,413,034*	*$3,506,538*	*$3,603,085*	*$17,843,440*

Figures in *italics* were revised during the evaluation.

a. Represents all incident mCRC patients. The population estimates from the panitumumab 2nd and 3rd line resubmission to the November 2013 PBAC meeting are used to estimate patient numbers.

b. Scenario B is likely an overestimate, as it has been assumed that all laboratories would conduct parallel testing. The most likely figure lies somewhere between the values presented here for Scenario A and B.

Source: Table 5.2-2, p58 of the SBA

Scenario B was used in the resubmission to the July 2014 PBAC meeting to estimate the net financial implications to the MBS. The resubmission to the July 2014 PBAC meeting also represented the steady state situation where all patients undergo *RAS* mutation testing after the prevalent pool of patients tested only for *KRAS* are retested as required.

The SBA assumed that currently all incident mCRC patients undergo *KRAS* mutation testing, and so the net cost of the requested change from *KRAS* to *RAS* mutation testing is that of *RAS* mutation testing for all incident cases plus a proportion of *RAS* mutation tests for those who previously had *KRAS* mutation testing only (and require *RAS* mutation testing to fulfil the PBS requirement of anti-EGFR antibody treatment).

The estimated net cost to the MBS for changing *KRAS* mutation testing to *RAS* mutation testing was approximately $2 million per year (see table below).

Estimated net implications to the MBS of *RAS* mutation testing (assuming listing as per Scenario B – a new item allowing concurrent or cascade testing of exons)

		Year 1	Year 2	Year 3	Year 4	Year 5
A	Base number of tests[a]	6046	*6218*	*6391*	*6567*	*6747*
B	Cost of *KRAS* mutation testing (MBS item 73330)	$230.95	$230.95	$230.95	$230.95	$230.95
C	Estimated cost of *KRAS* mutation testing (A × B)	$1,396,220	*$1,435,955*	*$1,476,105*	*$1,516,545*	*$1,558,300*
D	Cost of *RAS* mutation testing (all exons)	$526.95	$526.95	$526.95	$526.95	$526.95
E	Estimated cost of *RAS* mutation testing (A × D)	*$3,185,703*	*$3,276,364*	*$3,367,975*	*$3,460,244*	*$3,555,516*
F	Proportion *KRAS* WT	57%	57%	57%	57%	57%
G	No. patients who are *KRAS* WT (A × F)	*3446*	*3544*	*3643*	*3743*	*3846*
H	Proportion of patients previously having a *KRAS* mutation test who would require a *RAS* re-test	50%	25%	0%	0%	0%
I	Cost of *RAS* mutation testing (exc. *KRAS* exons 2, 3)	$296.00	$296.00	$296.00	$296.00	$296.00
J	Cost of *RAS* mutation re-testing[b] (G × H × I)	$510,003	*$262,258*	$ -	$ -	$ -
K	Estimated incremental cost of introducing *RAS* mutation testing in mCRC (E + J - C)	$2,299,485	*$2,102,668*	*$1,891,869*	*$1,943,699*	*$1,997,216*

Figures in *italics* were revised during the evaluation.
a. Represents all incident mCRC patients. The population estimates from the panitumumab 2nd and 3rd line resubmission to the November 2013 PBAC meeting are used to estimate patient numbers.
b. Assumes 50% of *KRAS* WT patients in year 1 and 25% of patients in year 2 who have already had *KRAS* mutation testing are tested for *RAS*.
Source: Table 5.2-3, p59 of the SBA

The net financial cost to government

The net financial implications to government for the listing of *RAS* mutation testing is presented in the table below. Net cost savings are estimated as the expansion of *RAS* mutation testing is outweighed by the decrease in anti-EGFR antibody treatment costs. The SBA estimated an offset of treatment duration of 12 weeks, as per the later-line panitumumab resubmission to the November 2013 PBAC meeting. These estimates may not be applicable to the *KRAS* exon 2 WT, *RAS* M+ population. Median PFS in *KRAS* WT patients treated with panitumumab in Study 408 was 12 weeks, however was only **(redacted)** in *KRAS* exon 2 WT, *RAS* M+ patients (see table with PFS results in Section 11). It is specifically these non-responding patients who will no longer receive treatment under the proposed listing and therefore it is appropriate that the cost-offsets are calculated based on their expected usage pattern. This may be a more reasonable estimate of treatment duration to apply. The base case financial implications to government have been respecified to incorporate this change (see table below), reducing the net cost savings to government by less than $10 million per year from the SBA's estimates.

Financial impact of modification to existing 2nd and 3rd-line panitumumab listing (including assessment group re-specification of the base case)

		Year 1	Year 3	Year 3	Year 4	Year 5
	Testing costs					
L	Cost of *RAS* mutation testing (Row K, previous table)	$2,299,485	*$2,102,668*	*$1,891,869*	*$1,943,699*	*$1,997,216*
	Treatment cost savings[a]					
M	Proportion receive ≥ 2 lines treatment	70%	70%	70%	70%	70%
N	Proportion *KRAS* WT	60%	60%	60%	60%	60%
O	EGFRi uptake	78%	80%	90%	90%	90%
P	*KRAS* EGFRi treated patients (Row A, previous table × M × N × O)	1981	*2089*	*2416*	*2482*	*2550*
Q	Proportion *RAS* WT	46%	46%	46%	46%	46%
R	*RAS* EGFRi patients (Row A, previous table × M × Q × O)	1525	*1609*	*1860*	*1911*	*1964*
S	*RAS* M+ who no longer receive EGFRi treatment (P – R)	456	*480*	*556*	*571*	*587*
T	EGFRi treatment cost (per 12 week treatment course)[b]	$(redacted)	$(redacted)	$(redacted)	$(redacted)	$(redacted)
U	*Assessment group re-specification: EGFRi treatment cost (per 7 week treatment course)[c]*	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)
V	Cost difference (based on SBA's assumptions) (S × T)	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)
W	*Cost difference (re-specified during the evaluation) (S × U)*	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)
X	Net to government (based on SBA's assumptions) (L + V)	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)
Y	*Net to government (re-specified during the evaluation) (L + W)*	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)	*$*(redacted)

EGFRi = anti-EGFR antibody; Figures in *italics* were incorrect in the SBA and corrected during the evaluation.
a. Utilisation estimates are based on those presented in the panitumumab resubmission to the November 2013 PBAC meeting. Treatment costs have been determined inclusive of the rebate paid under the special pricing arrangement which applies to panitumumab and cetuximab.
b. Cost of anti-EGFR antibody treatment in all patients (including *RAS* M+) (12 weeks) weighted by anti-EGFR antibody market share of panitumumab to cetuximab; in Year 1, 30:70, Year 2, 40:60 and Year 3+, 50:50 (inclusive of rebate)
c. Cost of anti-EGFR antibody treatment in *RAS* M+ patients (based on 7 weeks treatment duration, as re-specified during the evaluation) weighted by anti-EGFR antibody market share of panitumumab to cetuximab; in Year 1, 30:70, Year 2, 40:60 and Year 3+, 50:50 (inclusive of rebate).
Source: Table 5.2-3, p59 of the SBA

The assumption that all incident mCRC patients are currently undergoing *KRAS* mutation testing via the MBS is likely to be an overestimate. MBS item statistics for item 73330 indicate that, in 2013, 2,131 *KRAS* mutation tests were ordered. Compared to the SBA's estimate of total patients with mCRC in 2013 of 5,834, current uptake of *KRAS* mutation testing is approximately 37%. This could be due to the unavailability of anti-EGFR antibodies in the first-line setting, and it is likely that uptake of testing would increase if panitumumab is listed in the first-line. In consequence, the estimated cost offset of current *KRAS* mutation testing is likely to be overestimated, thereby underestimating the cost of *RAS* mutation testing to the MBS. This is tested in sensitivity analyses conducted during the evaluation; assuming only 37% of the offset in Year 5 increases the net cost to the MBS by approximately $1 million (see table below).

A sensitivity analysis was also conducted during the evaluation to explore the uncertainty regarding current testing offsets (assuming increased uptake of *RAS* mutation testing should anti-EGFR antibodies obtain a first-line PBS listing). The financial analysis is sensitive to this change, increasing the net implications to the MBS (and overall to government) by approximately $1 million per year. However, net cost savings were still observed in all years. This may still be an overestimate of savings because the SBA has not considered the cost of

re-testing beyond that required to review existing patients with incomplete *RAS* testing, re-biopsy or adverse events related to re-biopsy, should samples be insufficient for testing for all *KRAS* and *NRAS* exons in the financial implications to the MBS.

Sensitivity analysis conducted during the evaluation

	Year 1	Year 3	Year 3	Year 4	Year 5
Assuming uptake of current testing 37% (base case: 100%)					
Testing costs					
Incident mCRC cases	6046	*6218*	*6391*	*6567*	*6747*
Uptake of *KRAS* mutation testing	*37%*	*37%*	*37%*	*37%*	*37%*
Number of *KRAS* mutation tests offset	*2208*	*2271*	*2335*	*2399*	*2465*
Cost of *KRAS* mutation testing off set	*$510,001*	*$524,515*	*$539,181*	*$553,952*	*$569,204*
Cost of *RAS* mutation testing (Row E + Row J, second table in this section)	*$3,695,705*	*$3,538,623*	*$3,367,975*	*$3,460,244*	*$3,555,516*
Net cost of *RAS* mutation testing	*$3,185,704*	*$3,014,108*	*$2,828,794*	*$2,906,291*	*$2,986,312*
Treatment cost savings					
Cost difference (based on SBA's assumptions (Row V, previous table)	*-$7,384,264*	*-$7,776,672*	*-$8,978,961*	*-$9,224,948*	*-$9,478,943*
Cost difference (re-specified during the evaluation) (Row W, previous table)	*-$4,586,583*	*-$4,880,423*	*-$5,692,981*	*-$5,848,945*	*-$6,009,987*
Net to government (based on SBA's assumptions)	*-$4,198,559*	*-$4,762,564*	*-$6,150,167*	*-$6,318,657*	*-$6,492,631*
Net to government (re-specified during the evaluation)	*-$1,400,879*	*-$1,866,315*	*-$2,864,187*	*-$2,942,654*	*-$3,023,676*

Summary

- The net cost savings to government, as presented by the SBA, are likely to be overestimated by approximately less than $10 million per year, because the anti-EGFR antibody treatment offset in *KRAS* exon 2 WT/*RAS* M+ patients has been based on a treatment duration of 12 weeks.
- The net cost savings to government are likely to be overestimated by approximately $1 million per year, because it has been assumed that currently all patients undergo *KRAS* mutation testing. Currently, uptake of testing is approximately 37%. Should panitumumab be listed in the first-line setting, *RAS* mutation testing uptake is likely to increase.
- The costs associated with re-testing beyond that required to review existing patients with incomplete *RAS* testing, re-biopsy or adverse events related to re-biopsy, should samples be insufficient for the increased requirements for *RAS* mutation testing have not been considered in the SBA.
- With the first-line listing of panitumumab, there is a theoretical potential for testing to occur in patients who do not yet have metastatic CRC and thus for testing volumes to increase; this has not been considered in the SBA.

14. Key issues from ESC for MSAC

Extending *KRAS* mutation testing to *RAS* mutation testing

In the context of mCRC, the November 2013 MSAC meeting identified four questions which needed to be addressed about the co-dependencies between anti-EGFR antibodies and expanding the specific *RAS* mutations included in the biomarker definition.

- *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?*

ESC advice: from the tables in Section 11 above, particularly for first-line treatment, the effect is most likely operating as a class effect across anti-EGFR antibodies.

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

  ESC advice: from the tables in Section 11, and particularly with reference to the range of comparators (to which the anti-EGFR antibody was added in the treatment arm in five of the seven trials presented; it replaced bevacizumab in the other two trials) summarised in the footnotes, 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, noting that there are more clearly effective alternatives to anti-EGFR antibodies in earlier lines of therapy which may affect the consequences of this effect for an assessment of the health benefits and harms comparing anti-EGFR antibody based therapies with these alternative therapy options?*

  ESC advice: from the tables in Section 11, and requiring some extrapolation in the absence of data in these tables relating to later-line cetuximab, the effect appears consistent across all lines of therapy.

ESC noted caveats to the data presented in these tables in Section 11, including:

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

The conclusions of the Australian and European drug regulatory agencies (TGA and EMA, respectively) are consistent with the advice above; the Canadian and USA regulatory agencies are yet to reach a conclusion.

Overall, and as foreshadowed by PBAC and MSAC in November 2013, these findings support urgent amendments to the relevant MBS item descriptor to expand *KRAS* mutation testing to *RAS* mutation testing, coordinated with corresponding amendments to the relevant existing and proposed PBS restrictions for panitumumab and cetuximab.

- *What is the full spectrum of mutations which predict a reduced treatment effect of anti-EGFR antibodies, e.g.,* HRAS, BRAF, PIK3CA *mutations and others?*

  ESC advice: none of the other theoretically relevant mutations have yet been proven to predict variation in anti-EGFR treatment effect, or they have not yet been sufficiently analytically validated.

The November 2013 MSAC meeting also identified two questions which needed to be addressed about the practicalities of expanding *KRAS* mutation testing to include testing for other *RAS* mutations.

- *How and when can pathology laboratories modify their testing practices?*

  ESC advice: the logistics for *NRAS* mutation testing are essentially identical to *KRAS* mutation testing. Pathology laboratories can modify their testing practices quickly, and this will be driven by factors such as the relevant changes to the product information documents approved by the TGA for both panitumumab and cetuximab.

According to the SBA, 18 pathology laboratories currently offer *KRAS* mutation testing using eight different methods, including bi-directional DNA (Sanger) sequencing (the accepted gold standard when there is sufficient sample) in larger laboratories, commercial kits for allele-specific mutations in smaller laboratories and various multi-array, multiplex and Next Generation Sequencing options on the horizon. A survey of nine pathology laboratories in August 2013 for the SBA indicated that four laboratories were NATA-accredited to perform *NRAS* mutation testing and offered expanded *RAS* mutation testing. The RCPA has indicated that a quality assurance program (QAP) is being established for expanded *RAS* mutation testing, modelled on the existing QAP for *KRAS* mutation testing. The "Test-Tailor-Treat" website facility managed by Merck Serono in the context of cetuximab was expected to be restricted soon to laboratories offering full *RAS* mutation testing. The expectation is that awareness amongst oncologists and pathologists will drive demand for expanded *RAS* mutation testing in more laboratories.

The Pathology Services Advisory Committee (PSAC) has provided similar advice, indicating that more than 12 platforms were being used by NATA-accredited laboratories for *KRAS* mutation status and that most laboratories were already in the process of moving to offer expanding *RAS* mutation testing.

The critique agreed that laboratories would be able to move quickly to facilitate extended testing. It noted the high level of concordance (98.7%) across Australian laboratories for *KRAS* mutation testing, whether using Sanger sequencing or allele-specific methods. However with the rarer mutations encompassed by extended *RAS* mutation testing, some methods may be associated with a reduction in concordance for some samples where the quantity of relevant material falls below the method's limit of detection. This may increase the false negative rate, which would increase the proportion of patients not receiving anti-EGFR antibodies when appropriate. The critique recommended that MSAC consider whether defining the detection sensitivity thresholds of different *RAS* mutation testing methodologies would improve the overall clinical outcomes for patients with tumours containing low levels of *RAS* mutant cells. If so, MSAC should also consider the best way for this to be conveyed, such as the MBS item descriptor or via the QAP and NATA-accreditation practices already managed by the pathology community.

An issue raised for MSAC consideration in the critique is whether there should be an explicit limit to testing of metastatic tumour tissue rather than the current implied preference for testing such tissue. However, ESC noted that there would be practical and likely negative consequences for some patients of explicitly requiring metastatic tissue (such as those with metastases in the liver, in the brain or close to significant vasculature).

The pre-ESC response from the applicant addressed these issues, separating the limit of detection of an assay from the presence of molecular heterogeneity which may also explain a reduced concordance with rarer mutations. The pre-ESC response further separated molecular heterogeneity into spatial or intra-tumoural heterogeneity (where different parts of the same tumour may contain different mutations) and temporal or inter-tumoural heterogeneity (where mutation differences emerge with progression, in response to treatment and across the primary tumour and metastases). It argued that there is insufficient evidence to reliably distinguish between these sources of discordance and that reported mutation discordance rates usually fall within the assay error rate. It noted that *RAS* mutations can arise at any stage of tumour progression, and can therefore be homogeneous, heterogeneous (i.e., mosaic) or polyclonal; and that heterogeneity is more common in later disease after clones have been subjected to the selective pressure of earlier cytotoxic therapies. It concluded that current best practice is to test the most

recent sample available from each patient, but the decision of which sample to test should remain with the requesting clinician and the reporting pathologist. Accordingly it proposed that MSAC support the continued use of broad wording in the MBS item descriptor without specifying the test, the detection sensitivity or the source of the tumour tissue sample.

ESC advised that consensus was emerging to adopt broad wording for *RAS* mutation testing rather than listing specific mutations. The unintended negative consequences for some patients argue against specifying the source of tumour tissue for *RAS* mutation testing.

- *What is the most cost-effective way (for the MBS) to cover additional gene testing?*

  ESC advice: an economic evaluation confined to the proposal for extended *RAS* mutation testing compared to current *KRAS* mutation testing would result in dominance for *RAS* mutation testing because this would reduce the proportion of existing patients receiving additional panitumumab resulting in inferior health outcomes, and the increased costs of *RAS* mutation testing would be outweighed by the decreased costs of panitumumab. However this does not eliminate the obligation for a cost-effective implementation of this proposal.

  According to both the SBA and PSAC, there will be several pathways for extended *RAS* mutation testing, which separate mainly into simultaneous (concurrent, parallel) testing and sequential (tiered, cascade) testing. Simultaneous testing examines all relevant exons at the same time. Sequential testing examines some exons first (e.g., *KRAS* exon 2 and possibly *KRAS* exon 3), and if these are not mutated, reflexes to examine other exons (e.g., *KRAS* exon 4, and *NRAS* exons 2, 3 and 4, and *KRAS* exon 3 if not already examined).

  According to the SBA, the majority of surveyed laboratories indicated that they would prefer simultaneous testing of all six *KRAS* and *NRAS* exons. The SBA also presented alternative options of four separate MBS items for simultaneous and sequential testing, with different item descriptors and different fees. It further presented an option in the form of a "bridging" (or temporary) MBS item for those prevalent patients taking an anti-EGFR antibody but have only been tested for *KRAS* mutations.

  PSAC proposed a single MBS item which would allow either simultaneous or sequential testing. The item descriptor would most closely match the text of proposed items C or D in the SBA. It would have a single fee (of about $346) which would most closely match the fee (of $399.67) for proposed item D in the SBA, which also assumes a mix of simultaneous and sequential testing. However the basis for setting the fee in the SBA (a bottom-up approach with reference to the current fee for the existing MBS item for *KRAS* mutation testing) differs because the PSAC proposal is simply to increase this current fee (of $230.95) by 50% to cover additional *RAS* mutation testing, which increases it to a similar amount for EGFR mutation testing (of $397.35 for 4 exons).

  ESC noted that the fee for BRAF testing for one exon is also $230.95 and that a new primer is needed for each exon tested. Expanding from *KRAS* mutation testing to *RAS* mutation testing requires more primers to test more exons, but costs to prepare the sample for testing would not increase. The current wording does not specify which *KRAS* exons, so currently covers exons 2, 3 and 4. It is logistically identical to test *NRAS* exons 2, 3 and 4, so it is reasonable to assume a similar fee for this component.

  Overall, ESC agreed with PSAC in preferring a simple single MBS item for expanded *RAS* mutation testing. It suggested another possible basis for setting the fee by applying a

weighting based on the prevalence of *KRAS* exon 2 mutations, i.e., (43% x $230.95) + (57% x 2 x $230.95) = $362.59.

ESC considered that the costs of implementing and monitoring the proposed temporary item for prevalent patients would likely outweigh the intended savings by limiting it to exclude retesting of previously examined *KRAS* exons. The number of eligible patients would be small and rapidly diminish over time. ESC suggested that these patients instead be eligible for re-testing under the new *RAS* mutation test item.

Implications for mutation testing of extending the PBS reimbursement of panitumumab to include patients in the first-line setting

ESC noted that this was not discussed in the SBA, even though the survey presented in the SBA reported that 8% of *KRAS* mutation tests are currently performed on non-mCRC samples. ESC agreed with the critique that a shift to first-line panitumumab from the current later-line panitumumab may increase clinical pressure for earlier testing.

ESC advised that the questions of whether to restrict testing to metastatic tissue samples or to patients with metastatic CRC only remain unresolved. Relevant considerations here include how quickly the *RAS* mutation test result can be returned for a patient newly diagnosed with mCRC in the context of the timing of other factors influencing the start of appropriate treatment, and the consequences to the patient of any delay in starting treatment attributable solely to this turn-around time.

ESC further advised that, if MSAC agrees to retain the limitation of mutation testing to patients with metastatic CRC, for example because of a preference to conduct this testing on metastatic tumour tissue, then consideration might also be given to adding a note to the MBS item to indicate, but not mandate, this preference for the source of the tumour sample. Such a note could read: "[C]urrent best practice is to test the most recent tumour sample available, preferably from a metastatic tumour."

Financial implications

The SBA projects financial implications for each of its five scenarios, but utilised scenario B (two co-claimable items for a per testing unit cost of $526.95) as the base case in the parallel major resubmission to the July 2014 PBAC meeting. These projections include both components of the application (expand from *KRAS* to *RAS* mutation testing and expand panitumumab to first-line treatment). ESC noted that the SBA does not provide projections for the scenario where panitumumab is not approved for a first-line PBS listing.

ESC considered the SBA's projections as substantial overestimates for the following reasons:

- The projections assume an uptake rate of 100% which does not reflect the extent of uptake of the existing MBS item for essentially the same eligible population. Although there may be reasons for this discrepancy (e.g., *KRAS* mutation testing in public hospitals or in the context of clinical trials not being billed to the MBS, the rate of uptake may still be increasing as it becomes available across more laboratories, clinicians may have been hesitant to consider ant-EGFR antibodies due to emerging evidence that the biomarker definition needed expanding to reduce inappropriate prescribing), this suggests that the financial implications may be overestimated for each scenario.
- The projections adopt a fee for each scenario (ranging between $399 and $534) which is larger than either the fee suggested by PSAC or ESC ($346 or $362, respectively) which may be considered in any implementation of the requested listing.
- The costs to the MBS should be estimated on the basis of the rebate, not the MBS fee. The average rebate paid per service for item 73330 between January 2012 and December 2013 is $195.92, or 84.8% of the fee of $230.95.

- The costs to the MBS should be estimated as net costs by subtracting the costs of continuing with existing *KRAS* mutation testing. The SBA only presents total costs to the MBS.

The only aspect which contributes to a small underestimate is the costs of obtaining additional samples (and of any adverse effects of doing so) in the small and diminishing prevalent pool of patients not fully tested across all *RAS* exons.

Accordingly, ESC provided the following indicative estimates that would have been paid in previous years, based on the rates of MBS *KRAS* mutation testing, reflecting the ESC-suggested fee of $362.59 to reflect the increased unit cost of *RAS* mutation testing over *KRAS* mutation testing (rather than the greater fees in the SBA), and applying an 85% rebate to this fee.

	2012	**2013**	**Projected**
Number of tests	1,236	2,131	?
Current cost to MBS of *KRAS* mutation testing (actual claims)	$243,841	$415,819	?
Cost to MBS of *RAS* mutation testing (using 85% of $362.59)	$380,937	$656,777	?
Net cost to MBS of expanding *KRAS* mutation testing	**$137,096**	**$240,958**	**?**

These estimates are not projections, and do not account for re-testing (of a smaller prevalent pool than estimated in the SBA) or any additional testing of patients whose CRC is not diagnosed as metastatic, so more accurately reflect the modest costs that the MBS would have incurred in 2012 and 2013 if the MBS listing had been for expanded *RAS* mutation testing rather than *KRAS* mutation testing.

Overall, ESC supported a single MBS item to replace 73338, with a fee of approximately $362, as a cost-effective way to implement expanded *RAS* mutation testing on the MBS. ESC agreed that the MBS item should not specify the test methods (type of tumour tissue tested or whether *RAS* exons are tested simultaneously or sequentially), nor the detection sensitivity of the test. ESC also agreed that the new item should be available to patients previously tested under items 73330 or 73338.

15. Other significant factors

The table below summarises the main options for MSAC consideration. Transition options for patients previously tested for *KRAS* mutations only are discussed separately.

Descriptor component	SBA's nominated option	MSAC's alternative options
When to test		
CRC stage	limited to patients with metastatic CRC	exclude CRC stage from item descriptor
What to test		
Biomarker definition	Proposed wording: *'RAS* (Kirsten ras (*KRAS*) and neuroblastoma ras (*NRAS*)) gene mutations'	Proposed wording: *'RAS* gene mutations' Note: this wording is consistent with TGA approved/recommended changes, and would also include the option of *HRAS* gene mutation testing, or testing of additional *KRAS* and *NRAS* exons if future evidence is supportive of such testing
Type of tumour tissue tested	to remain *implied*, but not specified	limited to metastatic tumour tissue
Lower limit of detection for suitable *RAS* mutation tests	to remain not specified	specified in item descriptor or via QAP/NATA accreditation framework
Simultaneous or sequential testing of *RAS* exons	alternative options across five different MBS item scenarios	to remain not specified

ESC noted that the SBA did not propose how the biomarker definition in the MBS item descriptor might be updated efficiently in the light of any relevant new evidence in the future, or how the fee in the MBS might be updated with the advent of the new testing methods on the horizon, such as multiplex screening and Next Generation Sequencing.

16. Applicant's comments on MSAC's Public Summary Document

Amgen acknowledges the MSAC's positive recommendation for modifying the existing KRAS item code to allow RAS mutation testing. Amgen also welcomes the decision by MSAC that in the event that PBAC recommends that the PBS restriction of panitumumab or cetuximab be extended to include the first-line treatment of metastatic colorectal cancer, this MBS item descriptor would not require any further amendment to allow for earlier testing.

Amgen would like to highlight that the application for RAS testing was instigated by Amgen and granted fit-for-purpose status in July 2013 in the context of a 1st-line mCRC PBAC submission (the current application, 1363). This predated any consideration to the later-line setting and was not initiated by an urgent request from MSAC. In November and December 2013 Amgen and MSAC discussed the possibility of including in application 1363, a request to modify the existing KRAS item code in the context of later line EGFR inhibitor use. At this time, Amgen also proposed that that the change should occur for both panitumumab and cetuximab.

Amgen is disappointed with the MSAC's arrival at a fee of $362.59 which lacks methodology or substantiation, other than stating it is 50% higher than the existing KRAS fee. Amgen worked with the pathology community and using similar, existing MBS reimbursed molecular tests as a frame of reference, put forward 5 separate scenarios, discussing their various pros and cons. This $362.59 is lower than all 5 possibilities put forward and approximately $160 less than the base case utilised by Amgen, which was

chosen for the reason it satisfied the most criteria deemed relevant to implementation of such a test. It is also lower than similar, existing molecular tests which examine fewer exons, namely EGFR (4 exons with a fee of $397.50 versus at least 6 exons for RAS at $362.59).

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.