



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1362.1 - Cetuximab and KRAS mutation testing under MBS 73330

Applicant: Merck Serono 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

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

1. request changes to MBS 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); and
2. inform MSAC considerations of any implications on mutation testing of extending the PBS reimbursement of cetuximab to include patients in the first-line setting.

Merck Serono has lodged a concurrent submission to PBAC, scheduled for consideration at the November 2014 PBAC meeting, to:

1. request a modification of the existing second-line cetuximab 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 cetuximab 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 processes can be developed to ensure that extended *RAS* testing meets the same standards of *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 cetuximab or panitumumab 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 extraordinary circumstances had led to cancellation of the July/August 2014 MSAC meeting. 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 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 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 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 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 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 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 cetuximab resulting in inferior health outcomes, and the increased costs of *RAS* mutation testing would be outweighed by the decreased costs of cetuximab.

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 *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 that various options had been provided by the Pathology Services Advisory Committee (PSAC) and the Evaluation Sub-Committee (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 agreed that the application's financial estimates overestimate the net cost to the MBS of expanding from *KRAS* mutation testing to *RAS* mutation testing to the extent that they overestimate the extent of testing uptake, which has been lower than initially estimated. MSAC suggested that the indicative estimates previously provided by ESC would provide the Department with a basis for a lower estimate of 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. The application relied on a survey of (**redacted**) expert clinicians conducted in 2013 and the limitation of cetuximab treatment to patients with metastatic disease only to support its request not to change the tested population.

MSAC noted that the evaluation of the application identified two studies (Baldus et al. 2010; Malapelle et al. 2012), which reported lower *KRAS* prevalence rates (28% and 35.9%, respectively) for patients with stage I-II colorectal cancer compared to those with stage III (53% and 38%, respectively) and stage IV disease (45% and 41.8%, respectively). MSAC also noted that currently 8% of *KRAS* 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, given the urgency to consider its advice on amending the existing MBS item descriptor to allow full *RAS* mutation testing, and the relative clarity of the issues for testing in the context of extending the PBS restriction of either anti-EGFR antibody to include first-line treatment of metastatic colorectal cancer, that it would not be necessary to await the advice of ESC on this application.

4. Background

At its 51st meeting in December 2010, MSAC supported public funding of testing to determine *KRAS* mutation status of mCRC tumour material to determine eligibility for PBS-subsidised second line cetuximab treatment.

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 descriptor for *KRAS* mutation testing to allow access to panitumumab, as an alternative to cetuximab. On 1 April

2014, a new MBS Item (73338) was implemented to allow access to either cetuximab or panitumumab. This item replaces MBS Item 73330.

5. Prerequisites to implementation of any funding advice

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.

The applicant has already begun facilitating the uptake of *RAS* mutation tests.

- (redacted)
- (redacted)
- The applicant has been supporting the development of quality assurance protocols through the provision of reference samples, facilitating the exchange of samples between laboratories, and assisting some laboratories to upgrade their RT-PCR technology.

The applicant states that, by 30 July 2014, nine Australian laboratories (distributed across the country) were expected to be NATA-accredited and offering *RAS* mutation testing, with more laboratories to follow.

6. Proposal for public funding

The proposed item descriptor does not identify specific *RAS* mutations. The applicant suggested a single new MBS item descriptor using the term “RAS” would accommodate possible future changes to the biomarkers and avoid being unnecessarily restrictive in this emerging field.

Category 6 – Pathology Services Group P7 - Genetics
<p>73338</p> <p>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.</p> <p>Fee: \$230.95; Benefit: 75% = \$173.25, 85% = \$196.35</p>
<p>New Item Descriptor</p> <p>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 gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>Fee: \$411 to \$551</p>

The applicant recommended that the MBS item number be sufficiently permissive to allow laboratories to choose the most appropriate *RAS* mutation testing method for them, and to fix a price that allows the efficient use of existing accredited methods whilst encouraging transition to next generation sequencing technologies when batch sizes permit.

7. Consumer Impact Statement

MSAC is aware of concerns from the public about the current limited access to expanded *RAS* mutation testing. 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 have 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 cetuximab and panitumumab. Consumers have 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 applicant proposed that expanded *RAS* mutation testing would replace the current *KRAS* mutation testing funded under MBS item number 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).

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*.

The applicant 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. However, the applicant presented little information to address why the possibility of testing patients with CRC who do not have metastatic disease beyond noting that the average turn-around time of two weeks for testing would not unduly delay commencement of first-line metastatic CRC treatment. (redacted)

The applicant also anticipated the advent of next generation sequencing technologies, pointing out that “*panel tests could allow the consolidation of several MBS item numbers into one*” (para 1, p42, submission) and giving the example of a panel containing *EGFR* exons 19-22, *BRAF* exons 11 and 15, *KRAS* exons 2-4, *NRAS* exons 2-4, *PI3KCA* exons 9 and 20 being useful for non-small cell lung cancer (MBS item number 73328, 73327), melanoma (MBS item number 73336) and colorectal cancer (MBS item number 73330 and 73338). The applicant expected that the clinical requirement for fast turn-around times for expanded *RAS* tests in the first-line metastatic setting will drive a more rapid adoption of next generation sequencing technologies.

9. Other options for MSAC consideration

The table below summarises the main options for MSAC consideration.

Descriptor component	SBA's nominated option	MSAC's alternative options
When to test		
Disease stage	Limited to patients with mCRC with no leakage to non-metastatic CRC expected.	Exclude CRC stage from item descriptor.
What to test		
Biomarker definition	Proposed wording: ' <i>RAS</i> gene mutation status'. This would accommodate possible future changes to the biomarkers and avoid being unnecessarily restrictive.	' <i>RAS</i> (Kirsten <i>ras</i> (<i>KRAS</i>) and neuroblastoma <i>ras</i> (<i>NRAS</i>)) gene mutations'. Note: this wording is consistent with TGA approved changes and would enable the option of <i>HRAS</i> gene mutation testing.
Type of tumour tissue tested	To remain unspecified.	Limited to metastatic tumour tissue.
Lower limit of detection for suitable <i>RAS</i> mutation tests	The applicant does not specify a limit for the MBS item descriptor, but reports that a cut-off of 5% <i>KRAS</i> mutant allele frequency reflects current practice.	Specified in item descriptor or via QAP/NATA accreditation framework.
Simultaneous or sequential testing of <i>RAS</i> exons	Laboratories should be allowed to choose the most appropriate testing method	To remain unspecified.

10. Comparator to the proposed intervention

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.

11. 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.

12. Comparative effectiveness

The applicant noted that there are no published studies that compare the performance of Sanger sequencing (the evidentiary standard for *KRAS* exon 2) with BEAMing, pyrosequencing, WAVE Surveyor® or 454 technology in detecting *KRAS* exon 3-4 and *NRAS* exon 2-4 mutations. However, a comparison of pyrosequencing and Sequenom MassArray in the COIN trial demonstrated that 8,642 out of 8,719 (99.1%) of *KRAS* exon 2/3 mutation testing results were concordant (Maughan et al. 2011).

The applicant also noted that most methods employed by laboratories to detect *KRAS* and *NRAS* mutations beyond *KRAS* exon 2 are analytically equivalent and almost identical to the evidentiary gold standard for *KRAS* exon 2 analysis at a 5% limit of detection. Currently almost half of the diagnostic laboratories participating in the RCPA QAP use DNA sequencing (mostly Sanger sequencing, which has a 20-25% limit of detection) to detect *KRAS* mutations in Australia (RCPA QAP 2012, 2013). The high level of concordance

(98.7%) between laboratories, regardless of whether they use a commercial or an in-house method to detect *KRAS* mutations suggests that the number of patients receiving a false negative or a false positive result in the Australian clinical setting will be small.

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

The application included seven trials that provided progression-free survival (PFS) and overall survival (OS) data comparing treatment in *RAS* WT and *RAS* mutation-positive (M+) populations: FIRE-3, CRYSTAL, OPUS, PRIME, PEAK, Study 181, and Study 408. During the evaluation, additional six trials were identified that provided additional data for one or more *RAS* mutation subgroups: COIN, EPOC, NORDIC VII, CALGB/SWOG 80405, CO.17, and PICCOLO.

The applicant noted that the evidence for the predictive effect of *RAS* mutation status on the efficacy of cetuximab and panitumumab is still evolving and is retrospective in nature. Additionally, the sample sizes in some cases were small and clearly not powered to draw definitive conclusions.

Summary of progression-free survival (PFS) comparing treatment with anti-EGFR antibodies plus chemotherapy or best supportive care compared to chemotherapy with or without bevacizumab or best supportive care alone

Study	<i>KRAS</i> exon 2 WT population		<i>RAS</i> WT population		<i>KRAS</i> exon 2 WT, <i>RAS</i> M+ population		<i>RAS</i> M+ population		
	First-line treatment	Cmab	Comparator	Cmab	Comparator	Cmab	Comparator	Cmab	Comparator
<u>FIRE-3</u>	n	297	295	171	171	65	12.2	92	86
median PFS (months)		10.0	10.3	10.4	10.2	6.1		7.5	10.1
Difference in PFS		-0.3		+0.2		-6.1		-2.6	
HR (95% CI)		1.06 (0.88, 1.26)		0.93 (0.74, 1.17)		2.22 (1.28, 3.86)		1.31 (0.96, 1.78)	
<u>CRYSTAL</u>	n	316	350	178	189	32	31	246	214
median PFS (months)		9.9	8.4	11.4	8.4	7.2	6.9	7.4	7.5
Difference in PFS		+1.5		+3.0		+0.3		-0.1	
HR (95% CI)		0.67 (0.56, 0.87)		0.56 (0.41, 0.76)		0.81 (0.39, 1.67)		1.10 (0.85, 1.42)	
<u>OPUS</u>	n	82	97	38	49	15	16	92	75
median PFS (months)		8.3	7.2	12.0	5.8	7.5	7.4	5.6	7.8
Difference in PFS		+1.1		+6.2		+0.1		-2.2	
HR (95% CI)		0.57 (0.38, 0.86)		0.53 (0.27, 1.04)		0.77 (0.28, 2.08)		1.54 (1.04, 2.29)	
<u>COIN</u>		(KRAS exon 2/3 WT)							
n		362	367						
median PFS (months)		8.6	8.6						
Difference in PFS		0.0							
HR (95% CI)		0.96 (0.82, 1.12)							
<u>EPOC</u>	n	119	117						
median PFS (months)		14.1	20.5						
Difference in PFS		-6.4							
HR (95% CI)		1.48 (1.04, 2.12)							
<u>NORDIC-VII</u>	n	97	97					72	58
median PFS (months)		7.9	8.7					9.2	7.8
Difference in PFS		-0.8						+1.4	
HR (95% CI)		1.07 (0.79, 1.45)						0.71 (0.50, 1.03)	
		Pmab	Comparator	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator
<u>PRIME</u>	n	325	331	259	253	51	57	272	276
median PFS (months)		10.0	8.6	10.8	8.6	7.4	8.1	7.3	8.7
Difference in PFS		+1.4		+2.2		-0.7		-1.4	
HR (95% CI)		0.80 (0.67, 0.95)		0.73 (0.60, 0.88)		1.37 (0.90, 2.10)		1.31 (1.07, 1.60)	

Study	<i>KRAS</i> exon 2 WT population		<i>RAS</i> WT population		<i>KRAS</i> exon 2 WT, <i>RAS</i> M+ population		<i>RAS</i> M+ population		
PEAK	n	142	143	88	82	24	23		
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)		1.31 (0.66, 2.59)			
Later-line treatment	Cmab	Comparator	Cmab	Comparator	Cmab	Comparator	Cmab	Comparator	
CO.17							<i>(KRAS</i> exon 2 M+)		
n	110	105					75	76	
median PFS (months)	3.7	1.9					1.8	1.8	
Difference in PFS		+1.8					0.0		
HR (95% CI)	0.40 (0.30, 0.54)						0.99 (0.73, 1.35)		
	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator	
Study 181							<i>(KRAS</i> exon 2 M+)		
n	303	294	204	211	61	46	238	248	
median PFS (months)	5.9	3.9	6.4	4.4	3.7	3.7	5.3	5.4	
Difference in PFS		+2.0		+2.0		0.0		-0.1	
HR (95% CI)	0.73 (0.59, 0.90)		0.70 (0.54, 0.90)		0.89 (0.56, 1.42)		0.94 (0.78, 1.14)		
PICCOLO	<i>(KRAS</i> exon 2/3 WT)		<i>(KRAS/NRAS/BRAF/PIK3CA</i> WT)				<i>(Any mutant)</i>		
n	230	230	160	163					
number of progression 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)		
Study 408	n	124	119	72	61	11	11	95	111
median PFS (weeks)		12.3	7.3	12.3	6.9	7.1	7.6	7.4	7.3
Difference in PFS		+5.0		+5.4		-0.5		+0.1	
HR [95% CI]		0.45 (0.34, 0.59)		0.38 (0.27, 0.56)		0.81 (0.29, 2.26)		0.98 (0.73, 1.31)	

Comparator: FIRE-3 = bevacizumab + FOLFIRI; CRYSTAL = FOLFIRI; OPUS = FOLFOX; COIN = oxaliplatin plus capecitabine (66%) or FOLFOX (34%); EPOC = oxaliplatin plus capecitabine (25%) or oxaliplatin plus fluorouracil (75%); NORDIC-VII = Nordic FLOX; PRIME = FOLFOX; PEAK = bevacizumab + FOLFOX; CO.17 = best supportive care; 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 and CO.17).

Summary of overall survival (OS) comparing treatment with anti-EGFR antibodies plus chemotherapy or best supportive care compared to chemotherapy with or without bevacizumab or best supportive care alone

Study	<i>KRAS</i> exon 2 WT population		<i>RAS</i> WT population		<i>KRAS</i> exon 2 WT, <i>RAS</i> M+ population		<i>RAS</i> M+	
	Cmab	Comparator	Cmab	Comparator	Cmab	Comparator	Cmab	Comparator
<u>FIRE-3</u>	n							
median OS (months)	297	295	171	171	34	31	92	86
Difference in OS	28.7	25.0	33.1	25.6	16.4	20.6	20.3	20.6
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)		-0.3 1.09 (0.78, 1.52)	
<u>CRYSTAL</u>	n							
median OS (months)	316	350	178	189	32	31	246	214
Difference in OS	23.5	20.0	28.4	20.2	18.2	20.7	16.4	17.7
HR (95% CI)	+3.5 0.80 (0.67, 0.95)		+8.2 0.69 (0.54, 0.88)		-2.5 1.05 (0.86, 1.28)		-1.3 1.05 (0.86, 1.28)	
<u>OPUS</u>	n							
median OS (months)	82	97	38	49	15	16	92	75
Difference in OS	22.8	18.5	19.8	17.8	18.4	17.8	13.5	17.8
HR (95% CI)	+4.3 0.86 (0.60, 1.22)		+2.0 0.94 (0.56, 1.56)		+0.6 1.09 (0.44, 2.68)		-4.3 1.29 (0.91, 1.84)	
<u>COIN</u>		(<i>KRAS</i> exon 2/3 WT)		(<i>KRAS/NRAS</i> exon 2/3 <i>BRAF</i> WT)				(any <i>KRAS/NRAS/BRAF</i> M+)
median OS (months)	n	362	367	292	289		366	340
Difference in OS	17.0	17.9	19.9	20.1			12.7	14.4
HR (95% CI)	-0.9 1.04 (0.87, 1.23)		-0.2 1.02 (0.83, 1.24)				-1.7 1.00 (0.85, 1.18)	
<u>EPOC</u>	n							
median OS (months)	127	127						
HR (95% CI)	39.1	NR						
	1.49 (0.86, 2.60)							
<u>NORDIC-VII</u>							(<i>KRAS</i> exon 2 M+)	
median OS (months)	n	97	97				72	58
Difference in PFS	20.1	22.0					21.1	20.4
HR (95% CI)	+0.18 1.14 (0.80, 1.61)						+0.7 1.03 (0.68, 1.57)	
<u>CALGB/SWOG 80405</u>	n							
median OS (months)	559	578						
Difference in OS	29.0	29.9						
HR (95% CI)	-0.9 0.92 (0.78, 1.09)							

Study	KRAS exon 2 WT population		RASWT population		KRAS exon 2 WT, RAS M+ population		RAS M+		
	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator	
<u>PRIME</u>	n	325	331	259	253	51	57	272	276
median OS (months)		23.8	19.4	25.8	20.2	17.1	17.8	15.5	18.7
Difference in OS		+4.4		+5.6		-0.7		-3.2	
HR (95% CI)		0.83 (0.70, 0.98)		0.77 (0.64, 0.94)		1.39 (0.91, 2.13)		1.21 (1.01, 1.45)	
<u>PEAK</u>	n	142	143	88	82	24	23		
median OS (months)		34.2	24.3	41.3	28.9	NR	21.6		
Difference in OS		+9.9		+12.4					
HR [95% CI]		0.62 (0.44, 0.89)		0.63 (0.39, 1.02)		0.72 (0.28, 1.83)			
Later-line treatment		Cmab	Comparator	Cmab	Comparator	Cmab	Comparator	Cmab	Comparator
<u>CO.17</u>								(KRAS exon 2 M+)	
n		110	105					75	76
Median OS (months)		9.5	4.8					4.5	4.6
Difference in OS		+4.7						-0.1	
HR (95% CI)		0.55 (0.41, 0.74)						0.98 (0.70, 1.37)	
		Pmab	Comparator	Pmab	Comparator	Pmab	Comparator	Pmab	Comparator
<u>Study 181</u>	n	303	294	204	211	61	46	238	248
median OS (months)		14.5	12.5	16.2	13.9	11.3	9.2	11.8	11.1
Difference in OS		+2.0		+2.3		+2.1		+0.7	
HR (95% CI)		0.85 (0.70, 1.04)		0.80 (0.63, 1.02)		1.39 (0.91, 2.13)		0.93 (0.77, 1.13)	
<u>Study 408</u>	n	124	119	72	61	11	11	95	111
median OS (months)		8.1	7.6	8.1	7.5	6.2	5.2	5.2	4.4
Difference in OS		+0.5		+0.6		+1.0		+0.8	
HR [95% CI]		0.99 (0.75, 1.30)		1.03 (0.71, 1.48)		0.96 (0.37, 2.51) ^a		1.06 (0.79, 1.42)	
<u>PICCOLO</u>		(KRAS exon 2/3 WT)		(KRAS/NRAS/BRAF/PIK3CA WT)				(Any mutant)	
n		230	230	160	163				
number of deaths/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)	

Comparator: FIRE-3 = bevacizumab + FOLFIRI; CRYSTAL = FOLFIRI; OPUS = FOLFOX; COIN = oxaliplatin plus capecitabine (66%) or FOLFOX (34%); EPOC = oxaliplatin plus capecitabine (25%) or oxaliplatin plus fluorouracil (75%); NORDIC-VII = Nordic FLOX; CALBG/SWOG 80405 = bevacizumab + FOLFIRI (27%) or FOLFOX (73%); PRIME = FOLFOX; PEAK = bevacizumab + FOLFOX; CO.17 = best supportive care; 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 and CO.17).

13. Economic evaluation

The applicant derived a proposed fee for expanded *RAS* testing by inferring a ‘cost per exon’ from existing MBS items and then multiplying this by the increased number of exons to be tested. This approach yielded a range of proposed fees from \$411 to \$551.

However, the methodology used to derive the proposed fee contradicts assertions elsewhere in the application, e.g., “much of the manual work occurs prior to and following the sequencing run”, and “a sequential approach to testing will rapidly become obsolete as testing for *RAS* across exons 2 to 4 becomes standard practice”.

(redacted) Sensitivity analysis by varying the cost of the test from \$411.56 to \$531.96 was presented.

14. Financial/budgetary impacts

The financial estimates are based on past utilisation data for MBS items 73330 and 73338.

Financial impact to the MBS for *RAS* testing over first five years of listing

	Year 1	Year 2	Year 3	Year 4	Year 5
Additional retrospective tests (50% of <i>KRAS</i> exon 2 WT in Year 1, 25% in Year 2)	651	326	0	0	0
Increasing annual number of tests due extensions to EGFR-inhibitor PBS listings (10%)	2,387	2,626	2,888	3,177	3,495
Total annual number of <i>RAS</i> tests	3,038	2,952	2,888	3,177	3,495
Total annual cost of tests @\$531.96	\$1,616,094	\$1,570,346	\$1,536,300	\$1,690,037	\$1,859,200
Total annual cost of tests @\$471.76	\$1,433,207	\$1,392,636	\$1,362,443	\$1,498,782	\$1,648,801
Total annual cost of tests @\$411.56	\$1,250,319	\$1,214,925	\$1,188,585	\$1,307,526	\$1,438,402
Sensitivity analysis conducted during the evaluation					
Total annual cost of tests @\$362.59 (as proposed by ESC for 1363)	\$1,101,548	\$1,070,357	\$1,047,160	\$1,151,948	\$1,257,252
Total annual cost of tests @\$346.00 (as proposed by PSAC for 1363)	\$1,051,148	\$1,021,392	\$999,248	\$1,099,242	\$1,209,270
Increasing annual number of tests due extensions to EGFR-inhibitor PBS listings (20%)	2,604	2,865	3,151	3,466	3,813
Total annual cost of tests 20% growth @\$531.96	\$1,731,530	\$1,697,339	\$1,675,964	\$1,843,677	\$2,028,218
Total annual cost of tests 20% growth @\$471.76	\$1,535,579	\$1,505,257	\$1,486,301	\$1,635,034	\$1,798,692
Total annual cost of tests 20% growth @\$411.56	\$1,339,628	\$1,313,176	\$1,296,638	\$1,426,392	\$1,569,166
Total annual cost of tests 20% growth @\$362.59 (as proposed by ESC)	\$1,180,230	\$1,156,926	\$1,142,356	\$1,256,671	\$1,382,457
Total annual cost of tests 20% growth @\$346.00 (as proposed by PSAC)	\$1,126,230	\$1,103,992	\$1,090,089	\$1,199,173	\$1,319,204

The applicant concluded that the cost of *RAS* mutation testing is negligible compared to the cost of therapy for patients with mCRC. Reimbursement of *RAS* mutation testing through a new MBS item number will result in an annual cost to government of approximately \$1.3-

1.6M in Year 1, rising to \$1.4-1.9M in Year 5. However, these financial estimates do not capture likely increases attributable to population growth or increasing uptake of *RAS* testing irrespective of first-line PBS listings for cetuximab or panitumumab. Although utilisation of *KRAS* tests was lower than the maximum originally predicted by MSAC in 2010, the rate of use has continued to increase steeply (e.g., 30-fold increase from 2011/12 through to 2012/13). Thus the annual utilisation increase of 10% (allowed by the applicant to capture increased *RAS* testing associated with a first-line mCRC listing) is likely to be too low, overall.

15. Key issues from ESC for MSAC

This application was not considered by ESC. The allocated ESC discussant reviewed the material for the application and agreed that the key issues in application 1362.1 regarding changing the MBS item to accommodate expanded *RAS* mutation testing were consistent with application 1363.

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

Merck Serono appreciates the urgency with which MSAC have approved the amendment of Item 73338 to accommodate expanded *RAS* testing across all lines of treatment of mCRC. Expanding testing to include all *RAS* mutations and limiting subsidy of cetuximab to those patients demonstrated to have no *RAS* mutations both reduces harms and improves health outcomes.

17. Further information on MSAC

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