



Australian Government

**Medical Services Advisory Committee**

## **Public Summary Document**

### **Application No. 1172 – BRAF Genetic Testing in patients with melanoma for access to proposed PBS vemurafenib**

Applicant: Roche Diagnostics Pty. Ltd.

Date of MSAC consideration: 2 August 2012.

#### **1. Purpose of application**

In June 2011, the Department of Health and Ageing received an application from Roche Diagnostics Australia Pty Limited and Roche Products Pty Limited (Australia) requesting Medicare Benefits Schedule (MBS) listing of BRAF V600 testing for unresectable IIC or metastatic stage IV cutaneous melanoma to determine eligibility for treatment with vemurafenib, including through the Pharmaceutical Benefits Schedule (PBS).

#### **2. Background**

MSAC is currently considering an application for testing the V600 status in patients with locally advanced or metastatic melanoma for access to appropriate therapies. BRAF genetic testing is not currently eligible for reimbursement under the MBS, however, a small number of laboratories in Australia do offer the service for a fee.

#### **3. Prerequisites to implementation of any funding advice**

This application was deemed to propose a co-dependent package of two types of health technology (a pathology test and a medicine) subsidised through two different programs and therefore required advice from MSAC to be coordinated with that of the Pharmaceutical Benefits Advisory Committee (PBAC).

MSAC noted that regulatory approval by the Therapeutic Goods Administration (TGA) had been sought for the COBAS 4800 BRAF V600 mutation test, which is a trademarked real time PCR molecular diagnostic test, developed by Roche Diagnostics Pty Ltd, which identifies the V600E mutation (and has cross-reactivity with the V600K mutation) and was used to identify eligible patients in the key evidence (the BRIM 3 trial) supporting this application for MBS funding.

MSAC noted that the TGA regulatory framework for in vitro diagnostic (IVD) medical devices changed in July 2010, such that all IVDs now require premarket approval by the TGA unless they were offered prior to 1 July 2010 in Australia, whereby a transition period up to 2014 applies. As testing for BRAF mutations is currently only provided as an in-house IVD, it would be classified as a Class 3 in-house IVD. Any commercially available BRAF testing kits for the purposes of guiding therapy would, similarly, be classified as Class 3 IVDs.

#### **4. Proposal for public funding**

The application proposed the test of tumour tissue from a patient with unresectable stage IIIA, IIIB, IIIC or metastatic stage IV cutaneous melanoma to determine if the requirements relating to BRAF gene mutation status for access to vemurafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC noted that there were no proposals to pre-select a population of patients for testing based on tumour morphology or other characteristics.

#### **5. Consumer Impact Statement**

Key information from the decision analytic protocol for this assessment was made available to the public for consultation. Two responses were received and considered by PASC members.

#### **6. Proposed intervention's place in clinical management**

BRAF genetic testing, in addition to usual care, would be used to identify a subgroup of patients who, with unresectable stage IIIC or metastatic stage IV cutaneous melanoma, would likely benefit from treatment with vemurafenib. In the current management of metastatic melanoma without determination of BRAF genetic status, the majority of patients with these stages of disease receive dacarbazine - or less commonly fotemustine - as first-line chemotherapy, with or without a T cell immunostimulant (ie ipilimumab) or fotemustine as a second line treatment.

All patients with these stages of disease (unresectable stage IIIC or metastatic stage IV cutaneous melanoma) would be treated according to the results of BRAF genetic testing. Those with an eligible mutation would then be eligible to receive vemurafenib, while those who have no evidence of these mutations (and those who fail vemurafenib treatment) would receive dacarbazine or - less commonly - fotemustine chemotherapy. Those who failed these treatments would receive a T cell immunostimulant (ie ipilimumab) or fotemustine as subsequent therapy. Those who were considered unable to tolerate chemotherapy would be eligible for ipilimumab treatment.

#### **7. Other options for MSAC consideration**

MSAC noted advice from its Protocol Advisory Sub Committee to examine alternative scenarios in the decision analysis, which included:

1. for the tested population:

- also testing patients with unresectable stage IIIA disease, stage IIIB disease and resectable stage IIIC disease (the base case for the decision analysis), on the expectation that this reflects a greater than 50% likelihood that these patients will progress to disease for which vemurafenib would be eligible if test positive;
- also testing patients with resectable stage IIIA disease (ie testing all patients with stage III and IV disease), noting that this adds a group of patients with a lower likelihood of progressing; and
- testing all patients with unresectable stage III or metastatic stage IV melanoma, to enable a comparison with the population tested in the trial for the competing GSK2118436 BRAF inhibitor.

2. for the biomarker (where BRAF biomarker positive as detecting V600E or V600K is the base case for the decision analysis, reflecting the claim that V600K also predicts variation in the treatment effect of vemurafenib):

- defining BRAF biomarker positive as detecting V600E only, which restricts the definition to the V600 mutation primarily examined in the trial evidence generated for vemurafenib; and

- defining BRAF biomarker positive as detecting a V600 mutation without further qualification, which adds a small proportion of V600 mutations which might also predict variation in the treatment effect of vemurafenib.

## 8. Comparator to the proposed intervention

MSAC agreed that the nominated comparator of no BRAF testing was appropriate, and that a comparison of analytical performance of the alternative test options was also appropriate.

## 9. Comparative safety

MSAC noted that the submission identified a retest rate of between 0.4% and 9.4%. It is possible that for some patients, another biopsy may be required solely for the purpose of BRAF testing due to an inadequate amount of tumour tissue, poor quality of the first sample, or a need to test a new metastasis because of possible biomarker differences from the primary tumour. There is a small risk associated with this extra medical procedure that will vary according to site of the primary tumour or metastasis, which was not addressed in the submission.

## 10. Comparative effectiveness

MSAC focussed on the assessment of comparative analytical performance.

The cobas® 4800 BRAF V600 Mutation Test (a real-time PCR allele-specific assay; Roche Molecular Systems) was used in the BRIM3 trial of vemurafenib to determine BRAF V600 status. This was the evidentiary standard as defined in the Final DAP. However, although this technique is reported to be highly sensitive in detecting BRAF V600 mutations, it does not provide information on what that mutation is (i.e. V600E or V600K).

DNA sequencing and pyrosequencing (for resolution of discordant cases) was proposed by the submission as the analytical reference standard.

The submission only calculated diagnostic accuracy outcomes for two of the included studies (Halait et al., 2012 and Rueschoff et al., 2011). These studies assessed the ability of the cobas® test to accurately detect BRAF V600 mutations in formalin-fixed paraffin-embedded metastatic melanoma tissue samples. These samples were tested for BRAF V600 mutations using both the cobas® test and DNA sequencing. The samples with discordant results between the two tests were retested using pyrosequencing. The diagnostic accuracy outcomes for detecting BRAF V600 mutations and BRAF V600E or V600K mutations for all nine studies are shown in Table 1 and Table 2.

**Table 1 Diagnostic accuracy of BRAF V600 mutation testing methodologies to detect all BRAF V600 mutations compared to either the analytical reference standard (DNA sequencing with confirmatory pyrosequencing) or to DNA sequencing alone**

Study	BRAF V600 testing methodology		
	Allele-specific PCR	High resolution Melt	DNA sequencing
<b>Estimated Sensitivity</b>	[95% CI]		
Rueschoff et al (6) (cobas)	89.6% [85.2, 92.8] FN = 10.4% (29/278)		97.5% [94.7, 98.9] FN = 2.5% (7/278)
Halait et al (5) (cobas)	95.1% [91.4, 97.3] FN = 4.9% (12/245)		88.6% [83.7, 92.1] FN = 11.4% (28/245)
Ellison et al (7)	97.1% [89.0, 99.5] FN = 2.9% (2/69)		
Willmore-Payne et al		100% [89.3, 100]	

Study	BRAF V600 testing methodology		
	Allele-specific PCR	High resolution Melt	DNA sequencing
(4)		FN = 0% (0/41)	
<b>Estimated Specificity</b>			
Rueschoff et al (6) (cobas)	98.8% [95.4, 99.8] FP = 1.2% (2/171)		96.5% [92.2, 98.6] FP = 3.5% (6/171)
Halait et al (5) (cobas)	100% [97.6, 100] FP = 0% (0/193)		96.9% [93.0, 98.7] FP = 3.1% (6/193)
Ellison et al (7)	100% [95.7, 100] FP = 0% (0/108)		
Willmore-Payne et al (4)		91.8% [79.5, 97.4] FP = 8.2% (4/49)	
<b>Estimated Positive predictive value</b>			
Rueschoff et al (6) (cobas)	99.2% [96.8, 99.9] 1 – PPV = 0.8%		97.8% [95.1, 99.1] 1 – PPV = 2.2%
Halait et al (5) (cobas)	100% [98.0, 100] 1 – PPV = 0%		97.3% [94.0, 98.9] 1 – PPV = 2.7%
Ellison et al (7)	100% [93.2, 100] 1 – PPV = 0%		
Willmore-Payne et al (4)		91.1% [77.9, 97.1] 1 – PPV = 8.9%	
<b>Estimated Negative predictive value</b>			
Rueschoff et al (6) (cobas)	85.4% [79.5, 89.8] 1 – NPV = 14.6%		95.9% [91.5, 98.2] 1 – NPV = 4.1%
Halait et al (5) (cobas)	94.1% [89.8, 96.8] 1 – NPV = 5.9%		87.0% [81.6, 91.0] 1 – NPV = 13%
Ellison et al (7)	98.2% [92.9, 99.7] 1 – NPV = 1.8%		
Willmore-Payne et al (4)		100% [90.2, 100] 1 – NPV = 0%	

AS-PCR = allele-specific PCR, HRM = high resolution melt.

**Table 2 Diagnostic accuracy of BRAF V600 mutation testing methodologies to detect BRAF V600E or V600K mutations compared to either the constructed reference standard (DNA sequencing with confirmatory pyrosequencing) or to DNA sequencing alone**

Study	BRAF V600 testing methodology		
	Allele-specific PCR	High resolution Melt	DNA sequencing
<b>Estimated Sensitivity</b>			
		[95% CI]	
Rueschoff et al (6) (cobas)	90.5% [86.3, 93.6] FN = 9.5% (26/274)		97.4% [94.7, 98.9] FN = 2.6% (7/274)
Halait et al (5) (cobas)	95.8% [92.2, 97.9] FN = 4.2% (10/239)		89.1% [84.3, 92.6] FN = 10.9% (26/239)
Lopez-Rios et al (8) (cobas)	100% [90.4, 100] FN = 0% (0/46)		97.8% [87.0, 99.9] FN = 2.2% (1/46)
Miller et al (9)	100% [77.1, 100] FN = 0% (0/17)		
Ellison et al (7)	100% [93.2, 100] FN = 0% (0/67)		

Study	BRAF V600 testing methodology		
	Allele-specific PCR	High resolution Melt	DNA sequencing
Spittle et al (10)			100% [65.5, 100] FN = 0% (0/10)
Willmore-Payne et al (4)		100% [89.1, 100] FN = 0% (0/40)	
Hay et al (11)		100% [67.9, 100] FN = 0% (0/11)	
Pinzani et al (12)		100% [81.5, 100] FN = 0% (0/23)	
<b>Estimated Specificity</b>			
Rueschoff et al (6) (cobas)	98.3% [94.6, 99.6] FP = 1.7% (3/175)		97.1% [93.1, 98.9] FP = 2.9% (5/175)
Halait et al (5) (cobas)	98.0% [94.6, 99.4] FP = 2.0% (4/199)		97.0% [93.2, 98.8] FP = 3.0% (6/199)
Lopez-Rios et al (8) (cobas)	100% [92.7, 100] FP = 0% (0/62)		98.4% [90.2, 99.9] FP = 1.6% (1/62)
Miller et al (9)	71.4% [30.3, 94.9] FP = 28.6% (2/7)		
Ellison et al (7)	100% [95.7, 100] FP = 0% (0/110)		
Spittle et al (10)			100% [62.8, 100] FP = 0% (0/9)
Willmore-Payne et al (4)		92.0% [79.8, 97.4] FP = 8.0% (4/50)	
Hay et al (11)		100% [84.0, 100] FP = 0% (0/26)	
Pinzani et al (12)		100% [81.5, 100] FP = 0% (0/22)	
<b>Estimated Positive predictive value</b>			
Rueschoff et al (6) (cobas)	98.8% [96.3, 99.7] 1 – PPV = 1.2%		98.2% [95.5, 99.3] 1 – PPV = 1.8%
Halait et al (5) (cobas)	98.3% [95.4, 99.4] 1 – PPV = 1.7%		97.3% [93.9, 98.9] 1 – PPV = 2.7%
Lopez-Rios et al (8) (cobas)	100% [90.4, 100] 1 – PPV = 0%		97.8% [87.0, 99.9] 1 – PPV = 2.2%
Miller et al (9)	89.5% [65.5, 98.2] 1 – PPV = 10.5%		
Ellison et al (7)	100% [93.2, 100] 1 – PPV = 0%		
Spittle et al (10)			100% [65.5, 100] 1 – PPV = 0%

Study	BRAF V600 testing methodology		
	Allele-specific PCR	High resolution Melt	DNA sequencing
Willmore-Payne et al (4)		90.9% [77.4, 97.0] 1 – PPV = 9.1%	
Hay et al (11)		100% [67.9, 100] 1 – PPV = 0%	
Pinzani et al (12)		100% [82.2, 100] 1 – PPV = 0%	
<b>Estimated Negative predictive value</b>			
Rueschoff et al (6) (cobas)	86.9% [81.2, 91.1] 1 – NPV = 13.1%		96.0% [91.7, 98.3] 1 – NPV = 4.0%
Halait et al (5) (cobas)	95.1% [91.0, 97.5] 1 – NPV = 4.9%		88.1% [82.9, 92.0] 1 – NPV = 11.9%
Lopez-Rios et al (8) (cobas)	100% [92.7, 100] 1 – NPV = 0%		98.4% [90.2, 99.9] 1 – NPV = 1.6%
Miller et al (9)	100% [46.3, 100] 1 – NPV = 0%		
Ellison et al (7)	100% [95.7, 100] 1 – NPV = 0%		
Spittle et al (10)			100% [62.8, 100] 1 – NPV = 0%
Willmore-Payne et al (4)		100% [90.4, 100] 1 – NPV = 0%	
Hay et al (11)		100% [84.0, 100] 1 – NPV = 0%	
Pinzani et al (12)		100% [81.5, 100] 1 – NPV = 0%	

AS-PCR = allele-specific PCR, HRM = high resolution melt.

Overall allele-specific PCR and high resolution melt methods appear to be more sensitive than DNA sequencing methods in identifying patients with any BRAF V600 mutation (‘base case 1’ scenario) and patients with a BRAF V600E or V600K mutation (‘DAP base case’ scenario). Of the three studies that investigated the sensitivity and negative predictive values (NPV) of the cobas® test (the evidentiary reference standard), they were lower in the two larger studies, than in the smaller study or than the other small studies involving other allele-specific tests. This is due to the inability of the test to detect all BRAF V600 mutations and the increased likelihood of these mutations being present in a larger study population.

The false negative rates were low (less than 3%) in all except two studies comparing the cobas® test and DNA sequencing with confirmatory pyrosequencing (Halait et al., 2012 and Rueschoff et al., 2011). The median false negative rate of 4.9% (range 2.9-10.4%) for all studies reporting the detection of all V600 mutations by allele specific PCR test results was due to the inability of these tests to detect all V600K, V600D alternate V600E and other rare V600 mutations. The false negative rates of 2.5% and 11.4% for the two studies reporting the detection of all V600 mutations by DNA sequencing was primarily due to its inability to detect V600 mutations in tissue samples with <25% of cells containing BRAF mutations. The false negative rate for detection of V600E or V600K mutations varied between studies from

0% to 9.5% for allele-specific PCR methods; the number of false negatives depends on the number of V600K or alternate V600E mutations present in the sample population. Whereas all samples with V600E or V600K mutations were detected in the smaller studies, the two larger studies had 4.2% and 9.5% false negative rates (Halait et al., 2012 and Rueschoff et al., 2011). The false negative rates for the detection of V600E or V600K mutations by DNA sequencing ranged from 0% to 10.9%, this rate is dependent on the tumour sample quality. Thus, it is possible that one patient out of every ten to twenty who have metastatic melanoma containing a BRAF V600 mutation will miss out on potentially beneficial treatment with vemurafenib due to an inaccurate test result if it is assumed that vemurafenib is effective in patients who have a BRAF mutation on cobas testing but not on DNA sequencing.

The false positive rates were very low, less than 3.5% in all except two studies (Miller et al., 2004 and Willmore-Payne et al., 2005). In both of these studies mutations were detected by the test methods (allele-specific PCR and high resolution melt analysis), but not by the less sensitive DNA sequencing method. Thus, it is likely that a proportion of the cells in these false positive samples actually have a BRAF V600 mutation. In the remaining studies, few patients would be wrongly assigned, and the higher prevalence rates seen in these studies would have little impact on the positive predictive value in the Australian context. Nevertheless, the false positive rates indicate that up to four in every 100 patients that do not have BRAF V600 mutations will wrongly receive vemurafenib treatment and could have serious side-effects. Up to two out of every 100 that receive a positive result using an allele-specific test and three out of every 100 that receive a positive result with DNA sequencing will actually have BRAF wild type melanoma.

The submission states that most of the allele-specific PCR based methods are more sensitive than Sanger (DNA) sequencing in detecting the presence of cells containing BRAF V600 mutations in poor quality samples. Consequently, it recommends that for tumours with <25% tumour cell content an enrichment method (such as microdissection) or a more sensitive analytical method (e.g. allele specific PCR) should be used. This is reasonable. However, the recently reported heterogeneity of BRAF V600 mutation status among melanoma cells within a single tumour, also raises questions about test sensitivity. The more sensitive a BRAF V600 test is, the more likely it will positively identify tumours with low levels of cells with BRAF V600 mutations. However, it has not yet been determined whether there is a threshold ratio of BRAF V600 mutation to BRAF wild type melanoma cells that would predict a clinical response to targeted treatment (i.e. vemurafenib). Furthermore, as only 64.9% of BRAF V600K mutations were detected when using the cobas® test, at least one additional Australian patient in every hundred will receive a false negative result due to the increased prevalence of the BRAF V600K mutation in Australia compared with Europe and North America.

Overall, MSAC concluded that the test concordance data, and the test analytical validity data against the constructed reference standard (of Sanger sequencing with confirmatory pyrosequencing) suggests likely low levels of false positive and false negative test results from across the likely test options.

For allele specific PCR and Sanger sequencing, MSAC noted estimates of 90% and 98% sensitivity, 99% and 97% specificity, 99% and 98% positive predictive value and 85% and 96% negative predictive value, respectively, were calculated from the BRIM3 trial.

MSAC also noted that these estimates are generally consistent with the results of other published studies. MSAC noted that the low prevalence of the other V600 subtypes explains

why it is difficult to discern the difference between their inclusion and exclusion on comparative analytical performance.

MSAC accepted the interpretation of these data that up to 2% positive allele specific PCR test results and up to 3% positive Sanger sequencing results will have wild type melanoma and would receive vemurafenib to no benefit and the possibility of accelerated disease progression. However, MSAC considered that the lack of very effective alternatives means that the clinical and cost-effectiveness consequences of misallocation of treatment due to false positive test results are otherwise limited. The higher false negative rate means that one patient out of every ten to twenty patients with a test negative result will have a BRAF mutation and would not receive potentially beneficial treatment with vemurafenib.

MSAC was also reassured that pre-analytical processes such as formalin-fixed, paraffin embedded tissue and other aspects of the quality assurance program from the RCPA were well standardised which reduces the rate of discordant results in practice.

MSAC noted the overall integrated submission addressed comparative effectiveness as mediated through vemurafenib in patients testing positive for BRAF, and that this was the subject of PBAC consideration.

#### **11. Economic evaluation**

MSAC noted that the proposed MBS fee per test ranged between \$285 and \$325, and potentially wider use of cheaper PCR-based testing may explain why these amounts are greater than the current fee for KRAS testing which is suggested as a benchmark.

MSAC noted the overall integrated submission addressed comparative cost-effectiveness as mediated through vemurafenib in patients testing positive for BRAF, and that this was the subject of PBAC consideration.

#### **12. Financial/budgetary impacts**

MSAC recalled that pathology is generally associated with high bulk billing rates, suggesting that out-of-pocket payments and Extended Medicare Safety Net consequences would be small.

#### **13. Key Issues for MSAC**

MSAC noted that the following matters were referred by the July 2012 PBAC meeting:

- the disease stage at which subsidised testing should occur
- the total number of tests
- the number of tests per patient reflecting the frequency of repeat testing
- the costs of testing per patient treated with vemurafenib, and
- the cost of testing for resistance.

PBAC had noted that the advice from MSAC on these issues would be important to reduce overall uncertainty. In addition, the prevalence of BRAF mutations in melanoma patients in Australia may be particularly important given the relatively high prevalence of melanoma in Australia compared to other countries.

#### **14. Other significant factors**

MSAC noted that this integrated application had been processed under pilot arrangements for co-dependent health technologies involving testing strategies to be considered for MBS listing by MSAC and medicines to be considered for PBS listing by PBAC. The committee acknowledged the efforts undertaken to date to assist it and PBAC undertake a coordinated assessment of this particular co-dependent package. As prior experience has been limited,

MSAC considered that its adoption of a structured approach to considering the test component of the co-dependent package would be useful for future applicants

#### **15. Summary of consideration and rationale for MSAC's advice**

MSAC noted that the submission defined a different population of patients with cutaneous melanoma for BRAF testing than the base case defined in the Decision Analytic Protocol (DAP) finalised by PASC, by including any BRAF V600 mutation in the definition of the biomarker and by proposing to test only when patients were in unresectable Stage IIIC or Stage IV metastatic cutaneous melanoma. The submission's proposed definition more closely reflected the characteristics of the testing and the participants in the key randomised trial for the co-dependent vemurafenib therapy (BRIM3).

MSAC discussed whether the definition of the biomarker should be limited to V600E mutations (as prespecified for BRIM3), to V600E or V600K mutations (noting that BRIM3 also randomised participants with V600K mutations – because the Cobas 4800 assay used in BRIM3 has some cross reactivity with V600K – and reported results for this subgroup), or to any V600 mutation. MSAC noted that the limited prevalence data available suggests that V600K may be more prevalent in Australia than in BRIM3 and that this might be explained by the exclusion of patients with brain metastases from BRIM3 and the greater rate of melanoma associated with sun exposure in Australia.

In the context of a more general set of issues to be considered when judging the optimal definition of the biomarker as recorded in its deliberations relating to application 1173 (EGFR testing to support first-line erlotinib), MSAC advised that the biomarker be defined simply as “BRAF V600 mutations”. It based this advice on the non-statistically significant trend towards a greater treatment effect in the exploratory analysis of the 57/675 (8%) participants in BRIM3 with V600K mutations and the rarity of other V600 mutations meaning that evidence of harm or benefit cannot be concluded from the 18/675 (3%) participants in BRIM3 who had neither a V600E nor a V600K mutation. In the absence of clear clinical utility data for the residual V600 mutation subtypes, MSAC accepted expert advice that there was *in vitro* data to support a conclusion that the other mutation subtypes also drive melanoma growth, and that a BRAF inhibitor stops this growth. In addition, MSAC accepted that there was a biological argument that these subtypes all have the same functional consequences and similar three-dimensional structures.

MSAC noted that its advice to define the biomarker broadly as “BRAF V600 mutations” would have consequences for the optimal testing strategy, noting that the proprietary allele specific PCR (Cobas 4800) test used in BRIM3 and preferred in the submission is not designed to detect other V600 mutations. However, if other testing strategies are adopted in an endeavour to identify other rarer V600 mutations, there would generally be enough resected tissue to avoid having to take a new sample from the patient (although the costs of retrieval – e.g., new slides from the same block or a new block – should be included in the costs of testing and the rate of re-testing per patient for the economic evaluation and to calculate the total number of tests for the financial analyses should be up to 9.4% as reported for Sanger sequencing, noting that the economic evaluation is not sensitive to this). MSAC concluded that the test concordance data, and the test analytical validity data against the constructed reference standard (of Sanger sequencing with confirmatory pyrosequencing) suggests likely low levels of false positive and false negative test results from across the likely test options.

For allele specific PCR and Sanger sequencing, MSAC noted estimates of 90% and 98% sensitivity, 99% and 97% specificity, 99% and 98% positive predictive value and 85% and 96% negative predictive value, respectively, were calculated from the BRIM3 trial.

MSAC also noted that these estimates are generally consistent with the results of other published studies. MSAC noted that the low prevalence of the other V600 subtypes explains why it is difficult to discern the difference between their inclusion and exclusion on comparative analytical performance.

MSAC accepted the interpretation of these data that up to 2% positive allele specific PCR test results and up to 3% positive Sanger sequencing results will have wild type melanoma and would receive vemurafenib to no benefit and the possibility of accelerated disease progression. However, MSAC considered that the lack of very effective alternatives means that the clinical and cost-effectiveness consequences of misallocation of treatment due to false positive test results are otherwise limited. The higher false negative rate means that one patient out of every ten to twenty patients with a test negative result will have a BRAF mutation and would not receive potentially beneficial treatment with vemurafenib.

MSAC was also reassured that pre-analytical processes such as formalin-fixed, paraffin embedded tissue and other aspects of the quality assurance program from the RCPA were well standardised which reduces the rate of discordant results in practice.

MSAC advised that the best estimate of the prevalence of BRAF V600 mutations for patients with metastatic melanoma in Australia is 45.8% (range 43.3% to 48.2%) based on two studies totalling 227 patients as reported in Table A (O).11.4 of the submission. MSAC considered that the lower prevalence of BRAF mutations in sun-exposed melanoma, and the greater incidence of sun-exposed melanoma in Australia compared with other countries, explained the lower prevalence of BRAF V600 mutations in Australian melanoma compared with prevalence estimates worldwide and in the BRIM3 trial.

MSAC considered that only testing patients with unresected Stage IIIC or Stage IV metastatic melanoma would have the advantage of lowering the number and costs of patients who would need to be tested per patient treated, and the total number and costs of extra tests, because some patients tested at an earlier stage may not progress to more advanced disease (e.g., if surgical treatment is successful). MSAC noted that PASC had deliberately limited its proposal to consider encompassing a wider population for testing to minimise the increase in the number and costs of tests per patient treated by suggesting only those subgroups of patients most likely to progress to a stage of melanoma for which vemurafenib subsidy is being sought.

In the context of a more general set of issues to be considered when judging the value of testing earlier as recorded in its deliberations relating to application 1173, MSAC advised that testing should be limited to patients with unresected Stage IIIC or Stage IV metastatic melanoma. MSAC noted that there was not a great urgency in knowing the test result to initiate treatment (with an expected minimum 2-week turnaround for conducting the testing) and that recent evidence suggests BRAF mutations are not founder events and that some studies show that BRAF mutation rates are higher in metastatic disease. For these reasons, MSAC considered it was appropriate to determine the BRAF status of metastases.

MSAC considered that BRAF testing was not proposed for prognostic use and that repeated BRAF testing was not required because it had no role in monitoring disease or treatment. MSAC also noted that obtaining tissue samples for BRAF testing was generally not expected to be an additional source of harm to patients.

MSAC noted that the submission did not present data on the relationship between mutant load of BRAF in a tumour sample and the treatment effect of vemurafenib. MSAC noted that this remains an area of uncertainty and is the subject of ongoing research. In the meantime, the detectable mutant load of the “evidentiary standard” test used in BRIM3 should be ascertained to define a benchmark against which to assess the consequences of using other test options which are able to detect greater or lesser loads. Given the rate of technological advances in gene testing methodologies, MSAC advised that, in the event that BRAF testing is listed on the MBS, this and other aspects of comparative test performance should be reviewed after two years to assess whether subsequently introduced test options are likely to materially affect the clinical and cost-effectiveness basis for supporting the listing.

MSAC considered that there was no test currently available for predicting or testing resistance to vemurafenib, and that it is probably too early to know what tests might be informative.

MSAC noted that the studies of prognosis did not suggest that BRAF mutation positive status is a significant predictive factor for overall survival. Preclinical data and biological plausibility from the drug development pathway provide the basis for the claim that differing BRAF V600 mutation status predicts a variation in the treatment effect of vemurafenib.

MSAC noted that the considerations above formed a basis for a resubmission from the applicant to address the matters referred to MSAC by the July 2012 PBAC meeting. MSAC expected that its responses to these matters should thus be sufficient to support a PBAC reconsideration alongside further information from the applicant to address PBAC’s other reasons to defer its consideration in July 2012. In particular, MSAC noted that a PBAC reconsideration would need to quantify the consequences of the different options considered, and the modelled economic evaluation would need to be structured to examine how these consequences would vary the results of the incremental cost per extra quality-adjusted life-year (QALY) gained. In particular, even small variations in the proportions of false positive test results and false negative test results will have clinical and cost-effectiveness consequences of the resulting misallocation of treatment, and the model needs to be able to examine these.

## **16. 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 BRAF testing to help determine eligibility for proposed PBS-subsidised vemurafenib in unresectable Stage IIIC or Stage IV metastatic cutaneous melanoma, MSAC deferred the application until its responses to PBAC’s requests for advice and further information from the applicant are considered by PBAC. If PBAC refers more matters to MSAC for advice, MSAC will reconsider these referrals.

If PBAC subsequently decides to recommend to the Minister that vemurafenib be listed on the PBS, MSAC will support an expedited process for its reconsideration to align its support for public funding of BRAF testing according to the circumstances recommended by PBAC.

In that event, MSAC foreshadowed that the item descriptor could be expected to be:

A test of tumour tissue from a patient with unresectable stage IIIC or stage IV metastatic cutaneous melanoma requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to BRAF V600 mutation status for access to vemurafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

### **17. Applicant's Response to Public Summary Document**

The PBAC and MSAC have accepted that there is a high clinical need for melanoma therapies. Roche has agreed with and addressed the testing issues identified in the advice from MSAC in the form of a Resubmission.

### **18. Context for decision**

This advice was made under the MSAC Terms of Reference.

MSAC is to:

- Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:
  - the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
  - whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
  - the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
  - the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
  - other matters related to the public funding of health services referred by the Minister.
- Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.
- MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

### **19. Linkages to other documents**

MSAC's processes are detailed on the MSAC Website at: [www.msac.gov.au](http://www.msac.gov.au)