

**4.01 TRAMETINIB,  
500 MICROGRAM TABLET, 30, 2 MG TABLET, 30,  
MEKINIST®, NOVARTIS PHARMACEUTICALS AUSTRALIA  
PTY LIMITED**

**1 Purpose of Application**

- 1.1 Trametinib has a Section 85 Authority required listing in combination with dabrafenib for the treatment of unresectable or metastatic melanoma in patients with BRAF V600 mutation.
- 1.2 The submission was lodged to fulfil the requirements of the Managed Entry Scheme (MES) under which trametinib was PBS-listed.

**2 Requested listing**

- 2.1 The submission was not seeking any changes in the restriction, which is summarised below, although a reduced effective price was applied, based on the updated clinical trial data and economic evaluation. Trametinib was TGA registered on 14 February 2014 for the following indications:
- In combination with dabrafenib for the treatment of patients with BRAFV600 mutation positive unresectable stage III or metastatic (stage IV) melanoma.
  - As a monotherapy for the treatment of patients with BRAFV600 mutation positive unresectable stage III or metastatic (stage IV) melanoma and in whom either there is intolerance to BRAF inhibitors or BRAF inhibitors cannot be used.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TRAMETINIB Tablet, 0.5 mg	90	3	\$6,605.97 (published) \$ [REDACTED] (effective)	Mekinist®
Tablet, 2 mg	30	3	\$8,759.04 (published) \$ [REDACTED] (effective)	
DABRAFENIB Capsule, 50 mg	120	3	\$5,888.32 (published) \$ [REDACTED] (effective)	Tafinlar®
Capsule 75 mg	120	3	\$8,759.04 (published) \$ [REDACTED] (effective)	

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<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial

<b>Restriction:</b>	Authority required
<b>Clinical criteria:</b>	Patient must be receiving PBS-subsidised dabrafenib concomitantly for this condition, AND Patient must not have had progressive disease when treated with a BRAF inhibitor.
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
<b>Treatment phase:</b>	Continuing
<b>Restriction:</b>	Authority required
<b>Clinical criteria:</b>	Patient must have previously been issued with an authority prescription for this drug, AND Patient must be receiving PBS-subsidised dabrafenib concomitantly for this condition, AND Patient must have stable or responding disease.
<b>Administrative Advice</b>	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

- 2.2 The submission stated that a price reduction of █████% in the effective DPMQ was required to achieve the stipulated ICER/QALY of \$45,000/QALY- \$75,000/QALY. The submission added that the extent of uncertainty regarding the cost-effectiveness, and cost-effective price, of trametinib following incorporation of the phase III clinical trial data has been significantly reduced (see Consideration of the evidence and Economic analysis below). As such, the submission maintained that the continued listing of trametinib at the revised cost-effective price should no longer be subject to a MES. The submission also stated that the base case proposed by the sponsor is tenable to avoid a managed exit situation.
- 2.3 The Secretariat noted that there is a note explaining the MES of trametinib in the *Schedule of Pharmaceutical Benefits*. The PBAC should consider removing this note if the Committee is of mind to decide that the MES requirements have been met and so the MES is completed.

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

### 3 Background

- 3.1 Trametinib was previously considered by the PBAC in March 2014 and was rejected on the basis that superior comparative effectiveness of trametinib in combination with dabrafenib over dabrafenib monotherapy had not been established (March 2014 PSD, paragraph 7.1) and in view of concerns with the reliability of the BRF113220 trial, the PBAC considered the ICER was not reliable (March 2014 PSD, paragraph 7.3). A resubmission in November 2014 received a positive recommendation for use of trametinib in combination with dabrafenib for the treatment of unresectable or metastatic melanoma.

- 3.2 The November 2014 submission was made on the basis of a cost-utility analysis comparing trametinib plus dabrafenib combination treatment to dabrafenib monotherapy. The clinical evidence in the November 2014 submission included incomplete results from the randomised phase III COMBI-D and COMBI-V trials. The PBAC considered the completed COMBI-D and COMBI-V trials would be more informative than the phase II BRF113220 trial, which was not designed as an efficacy trial (November 2014 PSD, paragraph 7.6).
- 3.3 The PBAC concluded that the claim of superior comparative effectiveness of trametinib was reasonable, but noted that the magnitude of the treatment effect was still uncertain, as was the duration of treatment benefit (November 2014 PSD, paragraph 7.7).
- 3.4 The PBAC considered that the structure of the model was reasonable, but the inputs used from the BRF113220 trial did not provide a robust basis for making a subsidisation recommendation. The PBAC consequently proposed re-specification of the model when final data from COMBI-D and COMBI-V would be available (November 2014 PSD, paragraph 7.9).
- 3.5 The PBAC advised a number of conditions to modify the proposed MES, which included detail on the re-specification of the model (November 2014 MSD, paragraph 5.11). The table below provides a summary of those conditions.

**Table 1: Summary of MES conditions for managed entry (November 2014 PSD, paragraph 5.11)**

Summary of MES conditions	Submission response/comment
Evaluation 2 should include an individual patient data (IPD) meta-analysis using final results of both arms of the three trials (BRF113220, COMBI-D, COMBI-V). If this approach was determined to be methodologically difficult, then the final COMBI-D trial results should be used.	The submission complied with the condition and provided an IPD meta-analysis of the three trials. The submission also provided a meta-analysis of aggregated results.
Evaluation 2 should be provided as soon as possible (and expected to be within two years) after maximal follow-up of the COMBI-D trial.	Evaluation 2 has been provided in less than two years.
The clinical evaluation for Evaluation 2 should formally report the meta-analyses for both PFS and OS using the standard graphics of Kaplan-Meier curves, and with standard reporting of results (log rank p-values, hazard ratios with 95% confidence intervals, medians, difference in medians etc.).	The submission complied with the condition.
Should the extent of benefit of trametinib modelled from BRF113220 fail to be realised in the final COMBI-D and COMBI-V results, then the sponsor would rebate the Commonwealth taking account of: <ul style="list-style-type: none"> <li>- The price reduction of trametinib would be calculated to maintain the current ICER/QALY of \$45,000/QALY - \$75,000/QALY with reduced clinical benefits.</li> <li>- The rebate would be based on the price reduction multiplied by script numbers between the date of listing and date of the price reduction after applying an interest rate deemed appropriate to the Commonwealth.</li> <li>- The repayment would apply to dabrafenib and trametinib.</li> </ul>	The submission complied with a reduction of the trametinib price to maintain an ICER/QALY of \$45,000 – \$75,000/QALY and noted that a price decrease of █████% was required.
The economic evaluation for Evaluation 2 should use direct meta-analysis IPD curves to estimate incremental PFS and incremental OS up to the median duration of follow-up across the two arms compared to the clinical evaluation, and then allow extrapolation modelling on both arms for both PFS and OS curves from this timepoint, i.e. no statistical adjustments for crossover.	The submission complied with the condition.
The PBAC considered that the other inputs in the model need not change for the economic evaluation in Evaluation 2, despite the fact that the associated biases are in favour of trametinib. These include (a) utilities for the progression-free health state and post-progression health state, (b) the costs of additional adverse effects, and (c) not adjusting for the trial populations excluding patients with brain metastases whilst including these patients in the requested PBS population.	The submission did not comply with this condition, see paragraphs 3.6 and 3.7 below for details.

Source: compiled during the evaluation. AE=adverse event; PBAC=Pharmaceutical Benefits Advisory Committee; PBS=Pharmaceutical Benefits Scheme; PFS=progression-free survival; ORR=objective response rate; OS=overall survival.

- 3.6 The submission made the following updates to the economic model that were not requested by the PBAC:
- Treatment costs of post-progression anti-cancer therapy (PPACT) were included in the model. The inclusion of these costs had considerable impact on the ICER, favouring trametinib (see Economic analysis below).
  - Utility values were modified with updated ORR data and updated AE trial data and the way AE costs and incidence were modelled was changed. These changes had a small impact on the ICER, favouring trametinib.
  - Disease monitoring costs in the model were changed. This had a small impact on the ICER, favouring trametinib.
- 3.7 The submission stated that the above changes were consistent with best practice in health economics. The changes, particularly the case of post-progression therapy,

favoured combination therapy and did not necessarily follow best practice in health economics or model plausible costs.

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

#### **4 Clinical place for the proposed therapy**

- 4.1 Trametinib is a MEK inhibitor. The PBS restriction for trametinib for the treatment of unresectable or metastatic melanoma places its use as first-line for patients who are BRAF V600 mutation positive.
- 4.2 The submission did not discuss potential alterations in the clinical management algorithm as pertaining to combination therapy. However, the submission did note in its discussion of Quality Use of Medicines that the treatment landscape for melanoma had evolved in recent years, noting the approval of dabrafenib monotherapy, trametinib, and pembrolizumab. The submission noted that these new therapies have pushed ipilimumab into third-line therapy. Not mentioned was the positive PBAC recommendation of nivolumab in November 2015, although this was unlikely to affect the place of trametinib.

#### **5 Comparator**

- 5.1 Dabrafenib monotherapy was the main comparator, as it was in the November 2014 resubmission. This choice remains appropriate.

#### **6 Consideration of the evidence**

##### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

##### ***Consumer comments***

- 6.2 The PBAC noted that no consumer comments were received for this item.

##### ***Clinical trials***

- 6.3 The submission was based on individual and pooled results of the following trials:
  - BRF1132200 (N = 612), a phase II randomised, open-label trial comparing dabrafenib monotherapy to two different doses of trametinib in combination with dabrafenib;
  - COMBI-D (N = 423) a phase III randomised, double-blind trial comparing dabrafenib monotherapy to trametinib in combination with dabrafenib; and
  - COMBI-V (N = 704), a phase III randomised, open-label trial comparing vemurafenib monotherapy to trametinib in combination with dabrafenib.

6.4 Details of the trials presented in the submission are provided in the table below and key features of the trials are in the table following.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
BRF113220	An Open-Label, Dose-Escalation, Phase IB/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma (Part C).  Flaherty, K. T., Infante, J. R., Daud, A., Gonzalez, R., Kefford, R. F., Sosman, J., & Weber, J. (2012). Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations	September 2014  NEJM 2012 367(18), 1694-1703.
COMBI-D	A Phase III, randomised, double blind study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation positive cutaneous melanoma.  Long, G.V., Stroyakovskiy, D., Gogas, H., Levchenko, E., de Braud, F., Larkin, J (2015). Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, Phase 3 randomised controlled trial.	March 2015  Lancet 2015 386 (9992), 444–451.
COMBI-V	A Phase III, randomised, open-label study comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation positive cutaneous melanoma.  Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib.	January 2015  NEJM 2015 372(1), 30-39.

Source: Table B.2-1, p21 of the submission.

**Table 3: Summary of key features of BRF113220, COMBI-D and COMBI-V**

Trial	N	Design	Risk of bias	Patient population	Primary outcome	Use in modelled evaluation
<b>Trametinib 2mg/day combined with dabrafenib 150mg/bd vs. dabrafenib 150mg/bd</b>						
BRF113220	162 <sup>a</sup>	R, OL, MC	High	First-line <i>unresectable stage III) or metastatic (stage IV) melanoma</i>	PFS	Parametric survival functions fitted to the pooled PFS and OS IPD data from all 3 trials; ORR and AE data also included.
COMBI-D	423	R, DB, MC	Low		PFS	
<b>Trametinib 2mg/day combined with dabrafenib 150mg/bd vs. vemurafenib 960mg/bd</b>						
COMBI-V	704	R, OL, MC Trial halted (Phase III)	High	First-line <i>unresectable stage III) or metastatic (stage IV) melanoma</i>	OS	

<sup>a</sup> Includes 54 patients randomised to trametinib 1mg in combination with dabrafenib 150mg/bd (regimen not directly relevant to the evaluation of treatment effect).

AE=adverse event; bd=twice daily; DB=double-blind; IPD=individual patient level data; MC=multi-centre; OL=open label; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R=randomised  
Source: compiled during the evaluation

- 6.5 BRF113220 remained significantly affected by crossover. COMBI-D did not allow crossover, and though COMBI-V did have a protocol amendment allowing crossover, all data presented dated from before crossover was allowed.
- 6.6 As requested by the PBAC, the submission pooled the survival data of the 3 trials using individual patient data (IPD) and presented Kaplan-Meier curves, hazard ratios and confidence intervals for the pooled PFS and OS. The submission used BRF113220 results with no statistical adjustments for crossover in the pooled analysis and noted that, though the results were contaminated by crossover, the relative small size of BRF113200 meant the inclusion of BRF113220 in the pooled results had little effect on OS and PFS results.
- 6.7 The pooled results in the current submission were based on the final analyses of the COMBI-D and COMBI-V trials and recent unreported results from BRF113220 with 44.5 months of follow up (as opposed to 33.5 months in the latest reported analysis). The results of the updated BRF113220 data with 44.5 months follow up were not formally reported as individual trial results. Consequently, hazard ratios, confidence intervals, and Kaplan-Meier curves were not available for the BRF113220 data that contributed to the pooled data analysis.
- 6.8 Outcomes assessment for PFS and progression was investigator-assessed in BRF113220, although blinded independent central review (BICR) was used as a sensitivity analysis. In COMBI-D, the primary analysis of PFS was investigator-assessed (the trial is double-blind). Outcome assessments for PFS were not blinded in COMBI-V, which was open-label.

### ***Comparative effectiveness***

- 6.9 Key survival results from the pooled analysis as well as updated individual trial results from COMBI-D are presented in the table below. Also included are results from the November 2014 submission to allow comparison of results across time and trials. The Kaplan-Meier curves from the pooled analysis for OS and PFS follow the table. The submission requested that the results of the pooled analysis be maintained commercial in confidence.

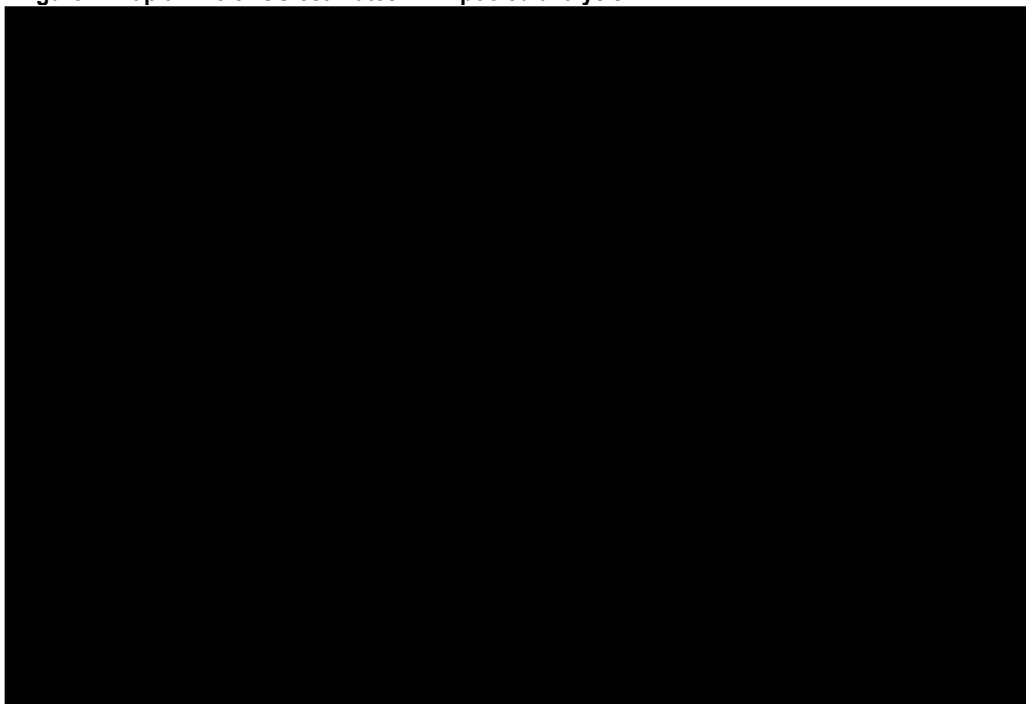
Table 4: Patient survival from the OS and PFS results based on the IPD pooled analyses for BRF113220, COMBI-D and COMBI-V and individual trial results

	Combination 150/2 therapy n/N (%)	Monotherapy n/N (%)	Absolute difference RD (95% CI)	Relative difference HR (95% CI)
<b>Current submission</b>				
<b>Progression-free survival – IPD pooled analysis</b>				
Pooled	NR		-	■ (■, ■)
Median months PFS (95% CI)	■ (NR, NR)	■ (NR, NR)	■	
<b>Overall survival – IPD pooled analysis</b>				
Pooled	NR		-	■ (■, ■)
Median months OS (95% CI)	■ (NR, NR)	■ (NR, NR)	■	
<b>Progression-free survival – COMBI-D</b>				
January 2015 cut-off <sup>a</sup>	72/211 (34%)	50/212 (24%)	10%	0.67 (0.53, 0.84)
Median months PFS (95% CI)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	2.2	
<b>Overall survival – COMBI-D</b>				
January 2015 cut-off <sup>a</sup>	112/212 (53%)	89/212 (42%)	11%	0.71 (0.55, 0.92)
Median months OS (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	6.4	
<b>November 2014 submission</b>				
<b>Progression-free survival – COMBI-D</b>				
26 Aug 2013 cut-off <sup>b</sup>	109/211 (52%)	103/212 (49%)	3%	0.75 (0.57, 0.99)
Median months PFS (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	0.5	-
<b>Overall survival – COMBI-D</b>				
26 Aug 2013 cut-off <sup>b</sup>	171/211 (81%)	157/212 (74%)	7%	0.63 (0.42, 0.94)
Median months OS (95% CI)	-(14.1, -)	-	-	-
<b>Progression-free survival – BRF113220</b>				
31 May 2012 cut-off <sup>c</sup>	23/54 (43%)	7/54 (13%)	30%	0.39 (0.25, 0.62)
Median months PFS (95% CI)	9.4 (8.6, 16.7)	5.8 (4.6, 7.4)	3.6	-
<b>Overall survival – BRF113220</b>				
31 May 2012 cut-off <sup>c</sup>	40/54 (74%)	35/54 (65%)	9%	0.67 <sup>d</sup> (0.34, 1.34)
29 March 2013 cut-off <sup>e</sup>	28/54 (52%)	23/54 (43%)	9%	0.73 (0.43, 1.24)
15 January 2014 cut-off <sup>f</sup>	22/54 (41%)	18/54 (33%)	7%	0.79 (0.49, 1.27)

Source: Tables B.6-1 and B.6-2, p73-74 of the submission. CI=confidence interval; IPD=individual patient data; NR=not reported; OS=overall survival; PFS=progression-free survival

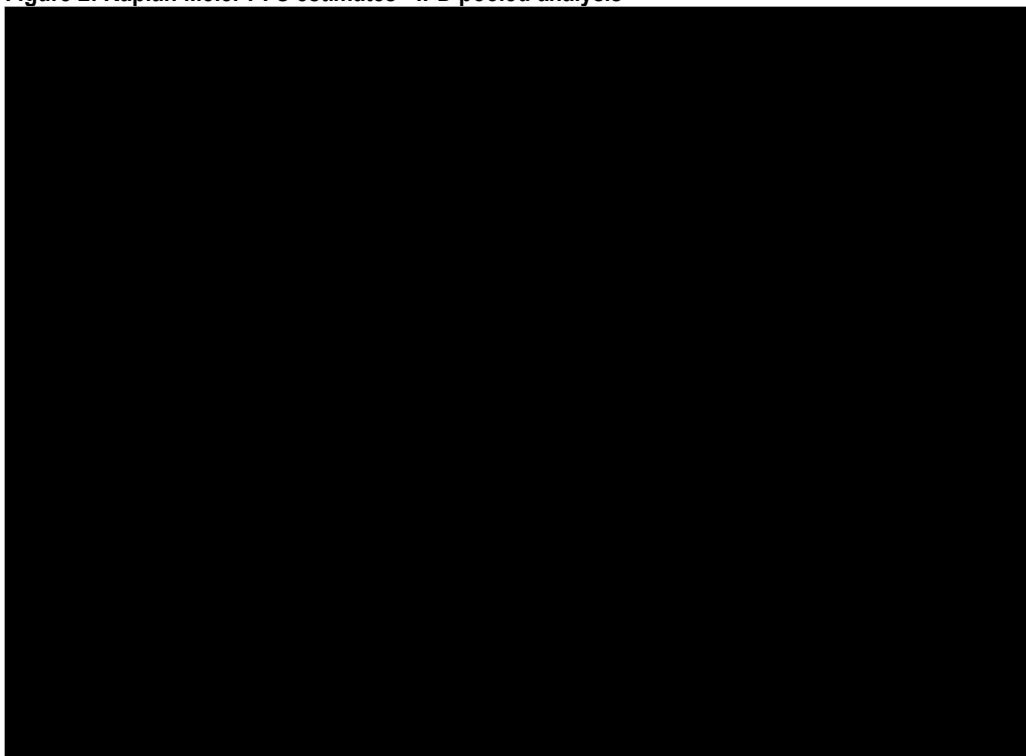
<sup>a</sup> median follow-up of 16 months in monotherapy and 20 months in combination therapy; <sup>b</sup> median follow up of 9 months; <sup>c</sup> median 14 months follow-up; <sup>d</sup> adjusted to ■ using RPSFT for use in the November 2014 model; <sup>e</sup> median 24 months follow-up; <sup>f</sup> median 33.5 months follow-up

**Figure 1: Kaplan-Meier OS estimates - IPD pooled analysis**



Source: Table B.6.2, p76 of the submission.

**Figure 2: Kaplan-Meier PFS estimates - IPD pooled analysis**



Source: Table B.6.9, p89 of the submission.

- 6.10 There were key differences in the survival results obtained in the current analyses and those presented in the November 2014 submission and used in the November 2014 model:
- The increase of the OS hazard ratio (lowering of estimated comparative efficacy) from █████ in the RPSFT crossover adjusted BRF113220 analysis applied in the November 2014 model to █████ in the IPD analysis of the 3 trials, which had no crossover adjustments.
  - The increase of the PFS hazard ratio (lowering of the estimated comparative efficacy) from 0.39 in the data presented in November 2014 for BRF113220 to █████ in the IPD analysis of the 3 trials.
- These differences indicated a reduction in clinical effect compared to that claimed in the November 2014 submission.
- 6.11 On a trial specific basis, OS hazard ratios (HRs) increased with more recent data cut-offs:
- In BRF113220, the unadjusted OS HR was 0.67 in May 2012, 0.73 in March 2013 and 0.79 in January 2014.
  - In COMBI-D, the OS HR was 0.63 in August 2012 and 0.71 in January 2015.
- 6.12 PFS data was not reported in later data cut-offs of BRF113220. COMBI-D showed a decrease in the PFS HR from 0.75 in August 2013 to 0.67 in January 2015.

### **Comparative harms**

- 6.13 A summary of adverse events (AEs) in BRF113220, COMBI-D and the combination arm of COMBI-V are provided in the table below. The submission did not provide AE results for the vemurafenib arm of COMBI-V because vemurafenib was considered to have a different safety profile to dabrafenib. Between-group differences in AEs for BRF113220 and COMBI-D were calculated during the evaluation.

Table 5: Summary of adverse events of special interest in BRF113220, COMBI-D & COMBI-V

	BRF113220			COMBI-D			COMBI-V
	Jan-14			Jan-15			Apr-14
	Mono N=53 n (%)	Combi N= 55 n (%)	Risk difference (95% CI)	Mono N=53 n (%)	Combi N= 55 n (%)	Risk difference (95% CI)	Combi N=350 n (%)
Pyrexia	17 (32)	41 (75)	0.42 (0.25, 0.6)	79 (37)	129 (62)	0.24 (0.15, 0.34)	200 (57)
Cardiac-related events	0 (0)	6 (11)	0.11 (0.03, 0.19)	10 (5)	12 (6)	0.01 (-0.03, 0.05)	29 (8)
Hepatic events	2 (4)	10 (18)	0.14 (0.03, 0.26)	25 (12)	39 (19)	0.07 (0, 0.14)	92 (26)
Ocular events	9 (17)	16 (29)	0.12 (-0.04, 0.28)	23 (11)	27 (13)	0.02 (-0.04, 0.08)	39 (11)
cuSCC <sup>a</sup>	9 (17)	4 (7)	-0.1 (-0.22, 0.03)	22 (10)	6 (3)	-0.08 (-0.12, -0.03)	5 (1)
Skin related toxicities	35 (66)	36 (65)	-0.01 (-0.18, 0.17)	112 (53)	101 (48)	-0.05 (-0.14, 0.05)	157 (45)
Diarrhoea	15 (28)	26 (47)	0.19 (0.01, 0.37)	33 (16)	63 (30)	0.15 (0.07, 0.22)	112 (32)
Haemorrhages	3 (6)	17 (31)	0.25 (0.12, 0.39)	32 (15)	40 (19)	0.04 (-0.03, 0.11)	62 (18)
Oedema	9 (17)	15 (27)	0.1 (-0.05, 0.26)	23 (11)	53 (25)	0.14 (0.07, 0.22)	63 (18)
Neutropenia	2(4)	10 (18)	0.14 (0.03, 0.26)	9 (4)	30 (14)	0.10 (0.05, 0.16)	50 (14)
Hypertension	2 (4)	6 (11)	0.07 (-0.03, 0.17)	36 (17)	54 (26)	0.09 (0.01, 0.17)	94 (27)
Hyperglycaemia	3 (6)	6 (11)	0.05 (-0.05, 0.16)	7 (3)	15 (7)	0.04 (0, 0.08)	23 (7)
Hypersensitivity	2 (4)	6 (11)	0.07 (-0.03, 0.17)	14 (7)	35 (17)	0.10 (0.04, 0.16)	36 (10)

Source: Table B.6-28, p125 of the submission. Combi=combination therapy; cuSCC=cutaneous squamous cell carcinoma; Mono=monotherapy

<sup>a</sup> including keratoacanthoma

- 6.14 Concerning AEs of special interest, the submission argued that the proportion of patients with pyrexia, decreased from 71% in the May 31 2012 BRF113220 data cut to 57% and 53% in the combination therapy arms of the COMBI-D and COMBI-V trials, respectively. The submission argued that this shift occurred due to the changes in management of pyrexia that occurred while the BRF113220 trial was underway. The submission pointed specifically to the recommendation to use corticosteroids and avoid dose reductions in cases of recurrent pyrexia and/or pyrexia accompanied with systemic manifestations. Though the risk difference was reduced for pyrexia in the COMBI-D trial, it remained substantial and statistically significant at RD=0.24. The increased risk in the combination arm of diarrhoea, oedema, neutropenia, hypertension and hypersensitivity was also statistically significant in the COMBI-D trial. In the monotherapy arm in COMBI-D, the only statistically higher AE was cutaneous squamous cell carcinoma. These results suggested that combination therapy may have inferior safety to monotherapy, which was the safety claim made in the March 2014 submission.

## Benefits/harms

- 6.15 A summary of comparative benefits and harms for combination therapy versus monotherapy is presented in the table below.

**Table 6: Summary of benefits and harms**

<b>Benefits</b>				
	<b>Combination 150/2 therapy</b>	<b>Monotherapy</b>	<b>Absolute difference</b>	<b>HR (95% CI)</b>
<b>Overall survival (pooled IPD analysis)</b>				
Died		NR		( )
Median mths (95% CI)	(NR, NR)	(NR, NR)		NR
<b>Progression-free survival (pooled IPD analysis)</b>				
Progressed		NR		( )
Median mths (95% CI)	(NR, NR)	(NR, NR)		NR
<b>Harms (COMBI-D January 2015)<sup>a</sup></b>				
	<b>Combination 150/2 therapy</b>	<b>Monotherapy</b>	<b>Risk difference (95% CI)</b>	
Pyrexia	129 (62)	79 (37)	0.24 (0.15, 0.34)	
Diarrhoea	63 (30)	33 (16)	0.15 (0.07, 0.22)	
Hepatic events	39 (19)	25 (12)	0.07 (0, 0.14)	

Source: Tables B.6-1 and B.6-2, p73-74, and B.6-28, p125 of the submission CI=confidence interval; IPD=individual patient data; mths=months

<sup>a</sup> No pooled comparisons were made for individual adverse events. COMBI-D was selected for comparative harms as it was the larger and most recent trial of the trials comparing dabrafenib monotherapy and dabrafenib in combination with trametinib

- 6.16 On the basis of the pooled individual patient data (IPD analysis), the comparison of combination trametinib and dabrafenib therapy with dabrafenib monotherapy resulted in:
- Approximately months difference in progression-free survival for 50% of patients.
  - Approximately months difference in overall survival for 50% of patients.
- 6.17 On the basis of the COMBI-D trial, for every 100 patients treated with combination therapy compared to dabrafenib monotherapy:
- Approximately 24 more patients will experience pyrexia.
  - Approximately 15 more patients will experience diarrhoea.
  - Approximately 7 more patients will experience hepatic events.

## Clinical claim

- 6.18 The submission concluded that combination trametinib and dabrafenib therapy is superior to dabrafenib monotherapy with respect to efficacy and has a different but no worse comparative safety profile.
- 6.19 This claim of superior comparative effectiveness had already been considered reasonable by the PBAC (November 2014 PBAC Minutes, paragraph 6.18), and the premise of this submission had been to establish the magnitude of incremental effect. The estimate of this effect, in terms of improvements in PFS and OS, was significantly reduced in the updated data provided in the current submission.
- 6.20 The key differences in the survival results applied to the economic evaluations of the current and previous submissions were:
- The increase of the OS hazard ratio (lowering of estimated comparative efficacy)

from [REDACTED] in the RPSFT crossover adjusted BRF113220 analysis applied in the November 2014 model to [REDACTED] in the IPD analysis of the 3 trials which had no crossover adjustments.

- The increase of the PFS hazard ratio (lowering of the estimated comparative efficacy) from [REDACTED] in the data presented in November 2014 for BRF113220 to [REDACTED] in the IPD analysis of the 3 trials.

- 6.21 While the PBAC previously relied on COMBI-V results for safety, in the current submission only results for the combination arm from COMBI-V were presented for safety outcomes, not allowing for any comparative assessment. The updated COMBI-D safety data indicated that, of the AEs of special interest, there were statistically significant higher rates of pyrexia, diarrhoea, oedema, neutropenia, hypertension, and hypersensitivity in the combination arm, while the only statistically higher AE in the monotherapy arm was cutaneous squamous cell carcinoma. This might go against the safety claim that combination therapy had a “different but no worse” safety profile compared to monotherapy. These results would suggest that the safety profile was in fact inferior, which was the claim made in the original March 2014 submission. The ESC noted that the Pre-Sub-Committee Response (PSCR) did not address the clinical issue of whether the updated safety data cast doubt on the safety claim that combination therapy had a “different but no worse” safety profile compared to monotherapy. The PBAC noted that this issue was not addressed.
- 6.22 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.23 The PBAC did not change its conclusions with respect to the comparative safety profile of combination trametinib with dabrafenib to dabrafenib monotherapy.

### ***Economic analysis***

- 6.24 The submission presented a cost-utility analysis based on pooled individual patient data from BRF113220, COMBI-D and COMBI-V, as specified by the PBAC in November 2014 (November PSD, paragraph 5.11). The table below provides a summary of the model structure.

**Table 7: Summary of model structure and rationale**

Time horizon	5 years in the model base case versus a follow-up of 44.5 months in BRF-113220, 16 months in the monotherapy arm and 20 months in combination therapy arm of COMBI-D and 10 months in the vemurafenib arm and 11 months in the combination arm of COMBI-V.
Outcomes	QALYs and life-years
Methods used to generate results	Kaplan-Meier curves generated from the IPD analysis are used up to median duration of follow-up, and then the log-logistic extrapolation of pooled BRF113220, COMBI-D and COMBI-V PFS and OS data is used.
Cycle length	1 week (no half cycle correction has been applied)
Transition probabilities	Derived from a series of observed and parametric survival functions. The model calculates the proportion of patients alive, and alive without progression, at each point (t) representing months since initiation of therapy, (OS(t) or PFS(t)). PFS(t) = the proportion of patients in the pre-progression state in each model cycle; PFS(t) – OS(t) = the proportion in the post progression state; and 1-OS(t) = the proportion dead.
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: compiled during the evaluation. IPD=individual patient data; PFS=progression-free survival; OS=overall survival

- 6.25 The model complied with most specifications of the PBAC, including the requirement to use Kaplan-Meier curves from the pooled IPD analysis to median follow-up and then apply extrapolation. Changes made to the economic evaluation that were not consistent with PBAC specifications included: updating of AE rates and costs; updating of monitoring costs; updating of pre-progression utility values; and most importantly, inclusion of post progression anti-cancer therapy (PPACT) costs. These latter costs had not been included in the previous model. While most changes did not affect the model considerably, the inclusion of PPACT costs favoured combination therapy significantly.
- 6.26 The submission included costs associated with PPACT use in the model because it argued these were clearly relevant to the current decision context as many therapies were reasonably effective in a second-line setting. Further the differential utilisation in the studies was likely to have influenced the observed OS outcomes upon which the submission was based, and consequently there was an intrinsic link between the OS outcome reported in the trials and the use of PPACT. The PSCR (p 1) argued that it is appropriate to include all relevant costs and consequences, and that the updated data showed that patients in the Phase III trials were managed with additional therapies post-progression, and therefore it is appropriate to include PPACT to demonstrate the true cost and value of combination therapy involving trametinib in Australia. The PSCR (p 2) also argued that the reason for not including these costs in Evaluation 1 (data from BRF113220 were immature, small differences in utilisation, adjustment for crossover in effectiveness estimates) did not apply to Evaluation 2 (which is based on mature COMBI-D and COMBI-V data which both had differences in PPACT utilisation).
- 6.27 The ESC advised that acceptance of PPACT costs would depend on whether the therapies in the model reflect likely current practice in Australia, especially when the inclusion largely changes the incremental costs of the model in favour of trametinib. The sponsor acknowledged (PSCR p. 2) that its approach was driven by “internal validity” (i.e. capturing the costs associated with the outcomes in COMBI-D and COMBI-V and that “the external validity of the modelling approach...is debateable”).
- 6.28 The submission calculated PPACT costs through the following steps:

- extracting percentages of specific PPACT use from COMBI-D;
- adjusting for censoring by dividing the proportion of patients using a specific therapy by the proportion of patients who progressed or died;
- estimating the dosage of each PPACT from the literature and product

information. For patients with weight-based dosing regimens, baseline data from the COMBI-D trial was used, and each second-line therapy was assumed to last 6 months (except the 4 doses of ipilimumab);

- obtaining course costs from the PBS schedule except for DTIC, vemurafenib and lomustine, which were not PBS listed.

Further details of these calculations are provided in Table 8.

**Table 8: Calculation of PPACT costs**

	Utilisation in COMBI-D		Utilisation in the model		Cost/dose	Cost/course	Expected cost	
	Mono	Combi	Mono*	Combi**			Mono	Combi
Ipilimumab	28%	18%	76%	66%	\$14,846.39	\$59,385.54	\$21,878.88	\$16,196.06
Dacarbazine	11%	8%	76%	66%	\$212.55	\$5,313.75	\$769.10	\$644.09
Vemurafenib	11%	8%	76%	66%	Same as dab	\$17,574.48	\$2,543.67	\$2,130.24
Paclitaxel	6%	4%	76%	66%	\$191.74	\$1,533.92	\$121.10	\$92.96
Fotemustine	4%	4%	76%	66%	\$1,167.00	\$9,336.00	\$491.37	\$565.82
Pembrolizumab	5%	2%	76%	66%	\$4,501.34	\$36,010.68	\$2,369.12	\$1,091.23
Carboplatin	3%	4%	76%	66%	\$158.57	\$1,268.56	\$50.07	\$76.88
Temozolomide	2%	5%	76%	66%	\$125.38	\$10,531.92	\$277.16	\$797.87
Dabrafenib	2%	4%	76%	66%	\$104.61	\$17,574.48	\$462.49	\$1,065.12
Cisplatin	3%	2%	76%	66%	\$118.37	\$710.22	\$28.04	\$21.52
Lomustine	2%	1%	76%	66%	Same as fote	\$9,336.00	\$245.68	\$141.45
Bevacizumab	2%	1%	76%	66%	\$3,552.67	\$42,632.04	\$1,121.90	\$645.94
<b>TOTAL</b>	<b>79%</b>	<b>61%</b>	<b>76%</b>	<b>66%</b>				

Source: Tables D.5—12, D.5—13 and D.5—14, p177, p179 and p180 of the submission.

\*adjusted for 76% of patients progressing or dying

\*\* adjusted for 66% of patients progressing or dying

dab=dabrafenib; fote=fotemustine

- 6.29 The ESC noted from the Commentary (4.01.COM.44) that it was difficult to determine what the adjusted percentages of utilisation for the model mean in terms of the specific use of each PPACT in patients who progress (because they are rates for the arm of the trial, not how they apply to individuals), and advised that the approach taken has likely overestimated the PPACT costs. Further, although this adjustment was stated to be “for censoring”, the approach taken appears to adjust also for patients who died before taking PPACT rather than those who just progressed.
- 6.30 The rates of utilisation of PPACT in the COMBI-D and COMBI-V were similar at the final cut-off of these trials to the most recent cut-off of the BRF113220 study for the monotherapy arm (51%, 43% and 46% respectively) and for the combination therapy arm (33%, 20% and 33% respectively). The PSCR (p 2) argued that it is reasonable for the estimated percentages of PPACT agent used to sum to more than these percentages of patient use because the different drugs may be used in combination or in sequence. However, the ESC noted that this would be affected by the assumption for the model that they all have the same duration of therapy (6 months), which does not account for variations in discontinuations or switches. The ESC also

queried whether the assumed duration of therapy (6 months) may also overestimate the PPACT cost offsets.

- 6.31 The ESC therefore advised that, even if the PBAC accepts that including the PPACT costs might be justified from an internal validity perspective (i.e. that the PPACT contributed to the overall survival observed in each arm), the way that these PPACT costs were calculated has resulted in significant uncertainty, as they did not capture the actual quantity of PPACT used by each patient.
- 6.32 Apart from not being requested by the PBAC, the estimates of PPACT use included in the model were not likely to reflect the current Australian treatment setting, and the method used to apply PPACT costs to the model inherently favoured combination therapy. The model was unlikely to reflect the current Australian treatment setting because COMBI-D was a multicentre international trial whose most recent data cut-off point was January 2015. Given the recent evolution of the treatment landscape in melanoma, the estimates were currently inappropriate. Specifically, with the listing of pembrolizumab and the PBAC recommendation of nivolumab, it is likely that ipilimumab, (the drug estimated to have the highest subsequent use in the model) might be relegated to third-line treatment or later. It is also likely that the other treatments included in the PPACT estimates will move into even later lines of treatment or may not be used at all. It would be reasonable to assume that a large proportion of patients would receive pembrolizumab, and since PBS listing, nivolumab. The submission acknowledged that the use of pembrolizumab by progressed patients in COMBI-D is likely to be underestimated, but the submission did not address the impact of this on the applied costs and outcomes of the PPACT component of the model. Pembrolizumab use has been addressed in a sensitivity analysis conducted during the evaluation (see below for results). It was also noted that DTIC, vemurafenib, paclitaxel, and bevacizumab, which were included by the submission in the PPACT use estimates, were not PBS-listed for melanoma. While the submission acknowledged that DTIC, vemurafenib and lomustine were not PBS-listed, it did not justify why costs for drugs that were PBS-listed, but do not have a restriction that allows treatment of melanoma, were included. The PSCR (p 3) stated that inclusion of bevacizumab, DTIC, vemurafenib and paclitaxel in the PPACT costs were appropriate to estimate the value of these health care resources, emphasising the “fact that these drugs are not listed for use in melanoma does not mean they are not used in this indication”. The ESC advised that although this might be a justification for the method of estimating costs, it also raises the issue of whether there is any evidence that these PPACT are effective, and noted that their inclusion may be artificially inflating costs of the comparator arm without any contribution to improving the health outcomes of the comparator arm.

6.33 The table below summaries the key drivers of the model.

**Table 9: Key drivers of the model**

Description	Method/Value	Impact
Updated survival estimates	Pooled individual patient data as requested by the PBAC. Kaplan-Meier curves generated from the IPD analysis are used up to median duration of follow-up, and then the log-logistic extrapolation of pooled BRF113220, COMBI-D and COMBI-V PFS and OS data was used.	High, favoured dabrafenib monotherapy
Inclusion of PPACT costs	Calculated from subsequent therapy estimates of the COMBI-D data. These costs were not requested by the PBAC.	High, favoured combination therapy

Source: compiled during the evaluation

6.34 The results of the base case of the economic evaluation are provided in the table below, followed by the results of the economic evaluation based on PBAC specifications.

**Table 10: Results of the economic evaluation**

Component	Combination	Monotherapy	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/extra QALY gained</b>			\$ [REDACTED]
<b>Trametinib 2 mg DPMQ needed to maintain incremental cost/QALY of \$45,000/QALY - \$75,000/QALY</b>			\$ [REDACTED]

Source: Table D.6-6, p187 of the submission. QALY=quality adjusted life year.

**Table 11: Adjusted results of the economic evaluation (following all specifications of the PBAC and excluding additional changes added in the submission)**

Component	Combination	Monotherapy	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/extra QALY gained</b>			\$ [REDACTED]
<b>Trametinib 2 mg DPMQ needed to maintain incremental cost/QALY of \$45,000/QALY - \$75,000/QALY</b>			\$ [REDACTED]

Source: Compiled during the evaluation. QALY=quality adjusted life year.

6.35 The significant discrepancy between the submission's base case and the results of the analysis requested by the PBAC were primarily due to the inclusion of PPACT costs.

6.36 If PPACT costs were retained in the model, as well as the other changes instituted by the submission (AE costs updated, pre-progression utilities updated, monitoring costs updated), but usage of pembrolizumab were increased from the submission's base case of [REDACTED]% in the monotherapy arm and [REDACTED]% in the combination arm to 90% in both arms; and the use of ipilimumab were decreased from [REDACTED]% in the monotherapy arm and [REDACTED]% in the combination arm to 10% in both arms (and 0% use of other therapies) the ICER/QALY would increase to \$45,000/QALY - \$75,000/QALY (required DPMQ of \$[REDACTED]). These results demonstrated the sensitivity of the model to PPACT costs and also indicated that the reduced DPMQ suggested by the submission (\$[REDACTED]) was likely to be an overestimate.

6.37 The ESC advised that inclusion of PPACT would depend on whether the therapies in the model reflect likely current practice in Australia. If not, then adjustments would be

required for the estimates of both costs and health outcomes to reflect likely clinical practice in Australia.

- 6.38 In summary, the ESC advised that several of the drugs included in the PPACT are not PBS-subsidised for the second-line treatment of melanoma, and that the recalculations were also based on the sponsor’s assumptions about the duration of PPACT (reflecting assumed standard protocols rather than actual utilisation in the trials), and on the published prices of PPACT, neither of which necessarily would apply (for example, ipilimumab is PBS-listed with a Special Pricing Arrangement).
- 6.39 Given these uncertainties, the ESC advised the PBAC to consider the appropriateness of including PPACT costs in the model, noting the PBAC’s previous views on the model when recommending the establishment of the MES, and the formal agreement by the sponsor to this approach in the Deed of Agreement. Given the PBAC recommendations for the trametinib MES (at its November 2014 meeting) were based on an ICER/QALY of \$45,000/QALY - \$75,000/QALY without the inclusion of PPACT in the model, it may not be appropriate to now subsequently adjust the model to include the PPACT and then back-calculate the post-MES price.
- 6.40 Table 12 below compares the current, proposed, and adjusted effective prices for both strengths of trametinib. The proposed prices include PPACT costs and the adjusted prices are based on PBAC specifications for the model and exclude additional changes to the model that were included in the submission (i.e. PPACT costs, changes to utilities and to adverse event and disease monitoring costs). Both the proposed and adjusted effective prices are the DPMQs required to maintain an ICER/QALY of \$45,000/QALY - \$75,000/QALY.

**Table 12: Current, proposed (PPACT included) and adjusted (PPACT removed) effective prices for both strengths of trametinib**

Strengths	Current prices		Proposed prices		Adjusted prices <sup>a</sup>	
	Ex-man	DPMQ	Ex-man <sup>b</sup>	DPMQ	Ex-man <sup>b</sup>	DPMQ
0.5mg (30 tabs)	\$ [REDACTED]	Not used	Not requested		-	
0.5 mg (90 tabs)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED] <sup>d</sup>
2 mg (30 tabs)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during the evaluation. DPMQ=dispensed price for maximum quantity; ex-man=ex-manufacturer; PPACT=post-progression anti-cancer therapy; tabs=tablets.

<sup>a</sup> The adjusted price is based on PBAC specifications for the model without additional changes made by the submission, which were inclusion of PPACT costs, changes to utility values, changes to modelling of adverse event costs and disease monitoring costs.

<sup>b</sup> The ex-manufacturer proposed and adjusted prices were back-calculated from the DPMQs and there may be rounding errors.

<sup>c</sup> The submission did not provide the current DPMQ for the 0.5 mg tablets; this was calculated during the evaluation based on the ex-manufacturer price.

<sup>d</sup> The adjusted price for 0.5mg was not calculated within the model as the 0.5mg dose was not used in the model. The price included here was for indicative purposes only and was based on the same percentage difference between the 2mg and 0.5mg price as in the submission's proposed effective price and current DPMQ (ie 75%).

<sup>e</sup> The submission identified this value as \$ [REDACTED], which was assumed to be a typographical error.

- 6.41 The ESC noted in the PSCR (p 5) that the sponsor had acknowledged an error in its estimate of the cost of dabrafenib in the model (i.e. dabrafenib price of \$ [REDACTED] instead of \$ [REDACTED]) and correcting this results in a price of \$ [REDACTED] for trametinib 2 mg tablet.

- 6.42 The PSCR (p 3 and 4) provided alternative estimates where the sponsor’s “analysis takes the observed utilisation of any PPACT regimen within the respective monotherapy and combination therapy groups in COMBI-D and assumes that this is all split 90:10 between pembrolizumab and ipilimumab monotherapy in Australia, without affecting patterns of overall survival.” The PSCR then argued that “Results of the analysis confirm the conservatism of the approach adopted in the submission, suggesting that the trametinib price associated with the requested ICER/QALY in this plausible scenario would be \$ [REDACTED] (based on the revised model) compared to \$ [REDACTED] in the base case.” The ESC noted that these recalculations were also based on the sponsor’s assumptions about the duration of PPACT and the published prices of PPACT, neither of which would necessarily apply (for example, ipilimumab is PBS-listed with a Special Pricing Arrangement).
- 6.43 The ESC therefore requested a recalculation of the trametinib prices based on the approach in the PSCR, but using effective rather than published prices for ipilimumab. The corrected dabrafenib price (\$ [REDACTED]) was therefore used to generate the prices of trametinib in Table 13 below.

**Committee-In-Confidence information**

**Table 13: Prices calculated using submission’s approach, but using effective rather than published prices for both strengths of trametinib**

	Prices calculated using submission’s approach, but using effective rather than published prices	
Strengths	Ex-man	DPMQ
0.5 mg (90 tabs)*	\$ [REDACTED]	\$ [REDACTED]
2 mg (30 tabs)	\$ [REDACTED]	\$ [REDACTED]

\* The submission did not include the price for trametinib 0.5 mg in its model; the price for trametinib 0.5 mg has been calculated following the same methodology used by the submission.

The table below provides results of a sensitivity analysis in the economic evaluation using effective prices and assuming the use of PPACT was restricted to 90% pembrolizumab, 10% ipilimumab with 0% use of other therapies.

**Table 14: Sensitivity analysis using effective prices for PPACT (assuming 90% use of pembrolizumab, 10% use of ipilimumab)**

Component	Combination	Monotherapy	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/extra QALY gained</b>			\$ [REDACTED]
<b>Trametinib 2 mg DPMQ needed to maintain incremental cost/ QALY gained of \$57,086</b>			\$ [REDACTED]

Source: Section D workbook.

Abbreviations: QALY=quality adjusted life year.

Note: costs were calculating by applying average PPACT costs calculated with effective prices as described in Table 12 above.

**End Committee-In-Confidence information**

**Drug cost/patient/course: \$ [REDACTED] for trametinib; \$ [REDACTED] for trametinib and dabrafenib combined.**

6.44 Cost per course per patient was calculated using the effective DPMQ of trametinib (and dabrafenib) assuming [REDACTED] packs per month multiplied by [REDACTED] months of combination therapy. The [REDACTED] months of therapy was generated by the economic model and was used in the submission’s financial estimates.

**Estimated PBS usage & financial implications**

6.45 This submission was not considered by DUSC. The submission maintained the same epidemiological approach to estimating PBS usage and financial implications. The submission maintained most of the same inputs as well, except for the following changes, consistent with those made in the economic evaluation:

- Updated AE rates and costs: the hospitalisation rates were higher than in the previous submission.
- The monitoring costs associated with combination treatment were reduced from the previous submission.
- PPACT costs were included, which were not requested by the PBAC. The PPACT costs did not likely reflect current practice in the Australian setting, and they unrealistically drove down the cost of listing combination therapy.

6.46 The table below provides a summary of estimated usage and financial implications for the PBS listing of trametinib based on the reduced effective price as well as the changes listed above. Estimates from the previous submissions are included for comparison.

**Table 15: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts <sup>a</sup>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts Nov 2014 <sup>a</sup>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts March 2014 <sup>a</sup>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated net cost to PBS/RPBS</b>					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS Nov 2014	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost PBS/RPBS March 2014	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Estimated net cost to the MBS</b>					
Net cost MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost MBS Nov 2014	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost MBS March 2014	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Estimated net cost to state governments</b>					
Net cost state/ territory gov't	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost state/ territory gov't March 2014 and Nov 2014	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Estimated total net cost</b>					
Net cost to government	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to gov't Nov 2014	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost gov't March 2014	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during the evaluation.

<sup>a</sup> Combined dabrafenib and trametinib scripts

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$20 - \$30 million per year.

- 6.47 While the number of treated patients had not changed since the November 2014 submission, the estimated number of scripts had increased given the anticipated increase in treatment duration ([REDACTED] months compared to [REDACTED] months in the November 2014 submission). This would have had a larger impact on costs to the PBS had the submission not included PPACT costs in the financial estimates which led to a significant underestimate of the costs to the PBS.
- 6.48 If PPACT costs were excluded from the financial estimates, total costs to government would increase to \$20 - \$30 million in Year 1 to \$30 - \$60 million in Year 5 for a total of more than \$100 million during the first 5 years of listing compared to the 5 year total of more than \$100 million estimated by the submission.

**Quality Use of Medicines**

- 6.49 The submission acknowledged that the treatment landscape for BRAF positive metastatic melanoma in Australia had undergone a rapid and marked transition recently from a landscape with few treatment options to a landscape with many treatment options.

**Financial Management – Risk Sharing Arrangements**

[REDACTED]

- 6.50 The sponsor also acknowledged that the existing risk-sharing arrangements for trametinib and dabrafenib would likely need to be updated as a result of the current submission.


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

**7 PBAC Outcome**

- 7.1 The PBAC recommended continuation of the Authority required listing of trametinib, for use in combination with dabrafenib, for the treatment of patients with BRAF V600 mutation positive unresectable stage III or metastatic (stage IV) malignant melanoma.

- 7.2 The PBAC recalled that, in recommending the listing of trametinib in November 2014, it had proposed to review the finalised results of COMBI-D and COMBI-V trials, to make sure patients receiving medicines on the PBS are being treated according to the best available evidence and that the cost of the combination therapy remains justified in terms of acceptable cost-effectiveness.
- 7.3 The PBAC also recalled that, in the terms of the MES for trametinib, should the extent of benefit of trametinib modelled from BRF113220 fail to be realised in the final COMBI-D and COMBI-V results, then the sponsor would rebate the Commonwealth taking account of:
- The price reduction of trametinib would be calculated to maintain the current ICER/QALY of \$45,000/QALY - \$75,000/QALY with reduced clinical benefits.
  - The rebate would be based on the price reduction multiplied by script numbers between the date of listing and date of the price reduction after applying an interest rate deemed appropriate to the Commonwealth.
- The repayment would apply to dabrafenib and trametinib.
- 7.4 The PBAC agreed with the ESC that most of the requirements of the MES for trametinib were met to the extent possible for the sponsor given the need for the revised model to rely on prices of other medicines which are confidential.
- 7.5 The PBAC accepted the inclusion of the PBS-relevant PPACT costs in the model. The PBAC recalled that it has accepted the inclusion of PPACT costs in its consideration of other medicines previously.
- 7.6 The PBAC noted the sponsor's acceptance that the calculation of PPACT costs is highly uncertain in terms of the duration of treatment, the current practice with treatment, the number of drugs used for treatment, and the choice of drugs.
- 7.7 Therefore, in deciding in principle to accept the inclusion of PPACT costs in the model, the PBAC did not accept that the inclusion of bevacizumab, DTIC, vemurafenib and paclitaxel in the PPACT costs was appropriate. The PBAC advised that bevacizumab, DTIC, vemurafenib and paclitaxel be removed from the model as these drugs are not listed on the PBS for the second-line treatment of melanoma as they have not been shown to be effective in this setting.
- 7.8 Accordingly, the PBAC also advised that the estimates of health outcomes in the model need not be adjusted.
- 7.9 The PBAC further advised that the estimates of PBS-listed PPACT should be adjusted to 90% pembrolizumab and 10% ipilimumab because this reflects the current status of the melanoma treatment algorithm and their PBS usage for the treatment of melanoma as acknowledged in the PSCR and in the pre-PBAC response.
- 7.10 The PBAC noted that special pricing arrangements applying to ipilimumab and pembrolizumab would need to be revealed to the sponsor for trametinib as its current assumptions of 50% of the list price for ipilimumab and pembrolizumab in the model are not correct. The PBAC noted that the sponsor had accepted that the effective prices of ipilimumab and pembrolizumab would need to be used in the adjusted

model of the PPACT costs.

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- 7.11 The PBAC noted that the submission estimated net overall expenditure to the PBS of approximately more than \$100 million over the first five years of listing. Noting the significant cost of the trametinib and dabrafenib combination in the financial estimates (\$30 - \$60 million per annum), the PBAC considered it appropriate to continue the risk sharing arrangement. However, the PBAC advised that the existing risk-sharing arrangement for trametinib and dabrafenib would need to be updated, based on the recommendations above for reducing the price of the combination.
- 7.12 The PBAC advised that, upon the sponsor's implementation of the reduction in price and other consequential changes, the MES information contained in the note of the *Pharmaceutical Benefits Schedule* for the listing of trametinib could be removed.
- 7.13 The PBAC recommended that the outcome of this MES be communicated to consumers and the medical profession particularly noting the overestimate of clinical benefit in the original submission.
- 7.14 The submission is not eligible for an Independent Review, because the PBAC has recommended that the listing be continued.

**Outcome:**

Recommended

**8 Recommended listing**

- 8.1 No change to the existing restriction. However, upon the sponsor's implementation of the PBAC recommendation (reduction in price and other consequential changes), the MES information contained in the note of the *Pharmaceutical Benefits Schedule* for the listing of trametinib could be removed.

**9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**10 Sponsor's Comment**

The sponsor had no comment.