

**6.04 DABRAFENIB,
Capsule 50 mg, 75 mg (as mesilate),
Tafinlar®;
and
TRAMETINIB,
Tablet 500 micrograms, 2 mg,
Mekinist®,
Novartis Pharmaceuticals Australia**

1 Purpose of Application

- 1.1 The submission requested an Authority Required (STREAMLINED) listing for dabrafenib (a BRAF inhibitor) in combination with trametinib (a mitogen-activated extracellular signal regulated kinase (MEK) inhibitor) as adjuvant treatment for BRAF V600 mutation positive patients with completely resected Stage III melanoma. This was the first submission to PBAC for dabrafenib+trametinib in this indication.
- 1.2 The submission was based on a cost-utility analysis of dabrafenib+trametinib compared with no active treatment in the proposed population. The key components of the clinical issue addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with resected Stage III melanoma with BRAF V600 positive mutations.
Intervention	Dabrafenib 150 mg twice daily in combination with trametinib 2 mg once daily until disease relapse or unacceptable toxicity, for a maximum of 12 months. Treatment must be adjuvant to complete surgical resection.
Comparator	Routine follow-up (consisting of clinician visits and radiological imaging). Nivolumab and pembrolizumab as near market comparators.
Main outcomes	Relapse-free survival, overall survival. The submission also presented outcomes of DMFS, FFR, AEs and SAEs and quality of life (EQ-5D).
Therapeutic claim	Dabrafenib in combination with trametinib is more effective than routine follow-up at improving relapse-free survival and overall survival, in patients with resected Stage III melanoma with BRAF V600 mutations. It is inferior in terms of safety to routine follow-up.

AE = adverse event; DMFS = distant metastases-free survival; FFR = freedom from relapse; SAE = serious adverse event

Source: Table1.1-1, p 5 of the submission

2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
DABRAFENIB				
75 mg capsule, 120	1	Initial: 3 Continuing: 5	\$8,763.21 (Published) \$ [REDACTED] (Effective)*	Tafinlar® Novartis Pharmaceuticals
50 mg capsule, 120	1	Initial: 3 Continuing: 5	\$5,892.49 (Published) \$ [REDACTED] (Effective)	Australia Pty Ltd

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TRAMETINIB					
2 mg tablet, 30	1	Initial: 3	\$8,763.21 (Published)	Mekinist®	Novartis Pharmaceuticals
		Continuing: 5	\$██████ (Effective)*		
500 microgram tablet, 30	3	Initial: 3	\$6,610.14 (Published)	Australia Pty Ltd	
		Continuing: 5	\$██████ (Effective)		

* A █████% reduction to the AEMP was proposed in the pre-PBAC response

Category/program	Authority required (STREAMLINED)
Severity	Resected Stage III
Condition	Malignant melanoma
Treatment phase	Initial treatment
Clinical criteria	The treatment must be adjuvant to complete surgical resection AND The condition must be positive for a BRAF V600 mutation AND Patient must have a WHO performance status of 1 or less AND Patient must be receiving PBS-subsidised trametinib and dabrafenib concomitantly for this condition AND The condition must not have been treated previously with PBS subsidised therapy
Population criteria	N/A
Treatment criteria	Treatment must commence within 12 weeks of complete resection AND Treatment must not exceed a maximum duration of 12 months (initial and continuing therapy) under this restriction

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Category/program	Authority required (STREAMLINED)
Severity	Resected Stage III
Condition	Malignant melanoma
Treatment phase	Continuing treatment
Clinical criteria	Patient must have previously been issued with an authority prescription for trametinib and dabrafenib concomitantly for adjuvant treatment following complete surgical resection AND Patient must not have experienced disease recurrence
Population criteria	N/A
Treatment criteria	Treatment must not exceed a maximum duration of 12 months (initial and continuing therapy) under this restriction

Category/program	Authority required (STREAMLINED)
Severity	Resected Stage III
Condition	Malignant melanoma
Treatment phase	Grandfathered patients
Clinical criteria	Patient must have previously received non-PBS subsidised drug for this condition prior to [list date] AND The treatment must be adjuvant to complete surgical resection AND The condition must be positive for a BRAF V600 mutation AND Patient must have a WHO performance status of 1 or less AND Patient must be receiving PBS-subsidised trametinib and dabrafenib concomitantly for this condition AND The condition must not have been treated previously with PBS subsidised therapy
Population criteria	N/A
Treatment criteria	Non-PBS subsidised treatment must have commenced within 12 weeks of complete surgical resection AND Treatment must not exceed a maximum duration of 12 months (initial and continuing therapy) under this restriction

- 2.1 The proposed amendments to the current restrictions for dabrafenib and trametinib for patients with unresectable Stage III or Stage IV malignant melanoma are presented below. The sponsor's proposed amendments are in italics and strikethrough. Flow on changes would also be expected for the programmed cell death 1 (PD-1) inhibitors (nivolumab and pembrolizumab) and ipilimumab, which are currently PBS listed for unresectable Stage III or Stage IV melanoma.

Dabrafenib	
Category/program	Authority required (STREAMLINED)
Severity	Unresectable Stage III or Stage IV
Condition	Malignant melanoma
Treatment phase	Initial treatment
Clinical criteria	The condition must be positive for a BRAF mutation, AND The condition must not have been treated previously with PBS subsidised therapy; OR Patient must have developed intolerance to another BRAF inhibitor of a severity necessitating permanent withdrawal, AND Patient must have a WHO performance status of 2 or less
Population criteria	N/A
Treatment criteria	<i>Patients who have progressed during treatment with a BRAF inhibitor are no longer eligible to receive PBS-subsidised dabrafenib</i>

Trametinib	
Category/program	Authority required (STREAMLINED)
Severity	Unresectable Stage III or Stage IV
Condition	Malignant melanoma
Treatment phase	Initial treatment
Clinical criteria	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.
Population criteria	N/A
Treatment criteria	<i>Patients who have progressed during treatment with a BRAF inhibitor are no longer eligible to receive PBS-subsidised trametinib</i>

- 2.2 The submission proposed a special pricing arrangement (SPA). Effective prices were used in the economic model and financial estimates. The PBAC noted that a [REDACTED] % reduction to the price (at the ex-manufacturer level) was proposed in the pre-PBAC response.
- 2.3 The ESC noted that the proposed listing included all completely resected Stage IIIA patients, irrespective of the size of lymph node metastases. The key trial, COMBI-AD, excluded patients with lymph node metastases ≤ 1 mm; therefore, there was no evidence to support adjuvant therapy in this patient subgroup.
- 2.4 The submission requested an amendment to the current PBS listings of both dabrafenib and trametinib to allow patients to be retreated with dabrafenib±trametinib in the unresectable setting, provided that patients did not experience disease progression whilst receiving adjuvant dabrafenib+trametinib treatment. Thus, patients who tolerate dabrafenib+trametinib and complete the 12-month adjuvant course would be eligible for retreatment with dabrafenib±trametinib for unresectable Stage III or Stage IV disease. The ESC advised that although not specifically proposed by the submission, patients with unresectable or metastatic disease who respond well to dabrafenib+trametinib therapy and then go on to have complete resection may also warrant access to adjuvant dabrafenib+trametinib therapy. The PBAC noted no data was presented to support this approach and that patients receiving dabrafenib±trametinib therapy under the Stage IV unresectable listing, who then subsequently undergo surgical resection, may still continue to access

dabrafenib±trametinib under the current unresectable listing, if the clinician deems it appropriate to continue treatment. The PBAC did not deem it therefore appropriate, without further data presented, for these patients to access dabrafenib+trametinib under the adjuvant listing, which should be reserved for patients who are naïve to dabrafenib+trametinib therapy.

- 2.5 The submission noted that a minor submission is scheduled for the March 2019 MSAC meeting to allow for the removal of the word ‘unresectable’ from the descriptor of MBS item 73336 for BRAF mutation testing for: ‘A test of tumour tissue from a patient with ~~unresectable~~ Stage III or Stage IV metastatic cutaneous melanoma’.
- 2.6 The ESC noted correspondence from MSAC to the PBAC on 11 February 2019 regarding sentinel lymph node biopsy (SLNB) and the implications for emerging adjuvant therapies. The MSAC noted that clinicians and other stakeholders have advised that all patients diagnosed by SLNB as being Stage IIIA or higher would now be referred to a medical oncologist and multi-disciplinary team to consider whether these patients should be offered systemic adjuvant treatment. The MSAC further noted that, compared to the 7th edition of the American Joint Committee on Cancer (AJCC) melanoma staging system (as used in COMBI-AD), the 8th edition staging system, which came into effect in Australia in 2018, has changed the proportions of patients classified into the various subcategories of Stage III, and that the risk of melanoma recurrence has also changed across these subcategories (see paragraph 6.9). In particular, more patients are now being classified as having Stage IIIA melanoma, and they may have a lower risk of recurrence than patients with Stage IIIB, IIIC or IIID melanoma. The MSAC advised the PBAC to review the proposed threshold of melanoma staging for the initiation of adjuvant treatment.
- 2.7 The MSAC also advised that the second Multicenter Selective Lymphadenectomy Trial (MSLT-II) demonstrated no improvement in 10-year survival with complete lymph node dissection (CLND) versus nodal observation in patients with a tumour-positive sentinel lymph node (Faries, 2017)*. As a result, some patients with a positive sentinel lymph node may no longer go on to an immediate CLND. This means that some patients will present for treatment with residual microscopically positive regional lymph nodes, whereas in the past (and in the COMBI-AD trial) this group would have undergone CLND.
- 2.8 In relation to the patient population, the PBAC foreshadowed that a recommended PBS listing of adjuvant dabrafenib+trametinib should be limited to patients with completely resected Stage IIIB, IIIC and IIID disease, as classified using the 8th edition of the AJCC melanoma staging manual, and that it should exclude patients with Stage IIIA disease. This was on the basis of:
 - Patients with Stage IIIA disease with metastases ≤ 1 mm being excluded from the COMBI-AD trial.

* Faries MB, Thompson JF, Cochran AJ, et al. Complete dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med.* 2017; 376: 2211-2222.

- Patients in the COMBI-AD trial with Stage IIIA disease with metastases > 1 mm having a relatively low risk of recurrence (29% after 3 years versus 57 to 82% for patients with Stage IIIB to IIID disease, Table 6), and the efficacy of dabrafenib+trametinib in these patients being uncertain (hazard ratio (HR) = 0.63; 95% confidence interval (CI): 0.26, 1.56, Table 6).
- Patients with Stage IIIA disease may now only have had sentinel lymph node biopsy demonstrating microscopic involvement, and the efficacy of dabrafenib+trametinib in these patients was unknown as 98% of patients in the COMBI-AD trial underwent a CLND.

The PBAC acknowledged that excluding Stage IIIA disease from adjuvant treatment may encourage immediate CLND as this enables improved staging. However, it was noted in the immediate CLND arm of the MSLT-II trial that non-sentinel node metastases were detected on pathological assessment in only 11.5% patients, and that CLND led to a change in disease stage in less than 6% of patients^{*†}.

- 2.9 The PBAC noted that, at 5 years in the nodal observation arm of the MSLT-II trial, 26.1% of patients had disease in non-sentinel nodes on the basis of ultrasonographic or physical examination, and this was statistically significantly higher than for the immediate CLND arm (19.9%, $p=0.005$). The PBAC considered patients classified as having Stage IIIA disease at the time of excision of the primary tumour, and hence not eligible for adjuvant treatment, should be eligible for adjuvant treatment if and when they meet the criteria for Stage IIIB, IIIC or IIID disease and undergo a salvage nodal resection. The PBAC noted the proposed PBS criteria require patients to commence adjuvant treatment within 12 weeks of complete resection.
- 2.10 Regarding PBS eligibility for patients who have not undergone CLND, noting that CLND was no longer standard of care for all patients with a positive sentinel lymph node, the PBAC considered that “completely resected disease” would, in practice, include all patients with a wide excision of the primary tumour and either CLND or sentinel lymph node biopsy (or both). The PBAC noted that, when the COMBI-AD trial was designed, CLND was considered standard practice and, as noted above, 98% of the trial participants had undergone CLND. Allowing treatment in patients without CLND thus impacts on the applicability of the trial results to the PBS population. However, it is currently unknown what proportion of patients will forgo a CLND as, although an improvement in melanoma-specific survival with immediate CLND dissection was not demonstrated in the MSLT-II trial, immediate CLND did increase the rate of regional disease control and provided prognostic information in terms of disease in non-sentinel nodes. The PBAC further noted the value of CLND is currently being debated in the clinical literature, and that immediate CLND is standard of care for patients presenting with clinically positive lymph nodes, and therefore more likely to be undertaken in patients with Stage IIIB, IIIC or IIID or Stage IV disease.

[†] Madu MF, Franke V, Bruin MM, et al. Immediate completion lymph node dissection in stage IIIA melanoma does not provide significant additional staging information beyond EORTC SN tumour biopsy criteria. *Eur J Cancer*. 2017; 87: 215-215.

For more detail on PBAC's view, see Section 7 PBAC outcome.

3 Background

Registration status

- 3.1 Dabrafenib in combination with trametinib was TGA registered in June 2018, under the priority review evaluation pathway, for the adjuvant treatment of patients with BRAF V600 mutation positive melanoma and involvement of the lymph node(s), following complete resection.
- 3.2 Dabrafenib monotherapy, trametinib monotherapy, and dabrafenib in combination with trametinib have also been TGA approved for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.

Previous PBAC considerations

- 3.3 Dabrafenib with or without trametinib combination is currently PBS listed for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or Stage IV malignant melanoma.
- 3.4 Nivolumab as adjuvant treatment for resected Stage III and Stage IV melanoma was rejected by PBAC in July 2018. Pembrolizumab as adjuvant treatment for resected Stage III melanoma was considered by PBAC in November 2018 and also rejected.

For more detail on PBAC's view, see Section 7 PBAC outcome.

4 Population and disease

- 4.1 Patients who have completely resected Stage III melanoma are at a high risk of developing unresectable disease recurrence, which, in many cases, includes distant metastases. Despite the availability of immunotherapies and targeted therapies for the treatment of unresectable or metastatic melanoma, unresectable disease remains associated with high mortality. To reduce the risk of relapse post resection, high-risk patients may be considered candidates for adjuvant treatment.
- 4.2 Patients with Stage III melanoma have disease involvement of the regional lymph nodes or the presence of in transit or satellite metastases.
- 4.3 In Australia, there are no agents currently available on the PBS for adjuvant treatment of melanoma. The Cancer Council of Australia (CCA) guidelines[‡] recommend adjuvant treatment of resected Stage III patients with pembrolizumab, nivolumab or dabrafenib+trametinib (only in BRAF positive patients because dabrafenib is a BRAF inhibitor). The guidelines acknowledge that, currently, patients can only access these treatments if they are eligible for a clinical trial or are self-funded. If patients develop unresectable Stage III or Stage IV melanoma, they are eligible for PBS-subsidised treatment with targeted therapy or immunotherapy depending on their BRAF mutation status. Patients whose tumour expresses BRAF mutations are eligible for

[‡] Carlino M, Atkinson V, et al. What is the role of adjuvant systemic therapy in patients with resected Stage II and Stage III melanoma? Sydney: Cancer Council Australia; 2018 [updated 6 August 2018].

BRAF inhibitor ± MEK inhibitor therapy (including dabrafenib±trametinib), followed by PD-1 inhibitors upon disease progression.

For more detail on PBAC's view, see Section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated observation (routine follow-up consisting of clinician visits and radiological imaging) as the main comparator. Pembrolizumab and nivolumab were nominated as near-market comparators. The ESC considered that the nominated comparators were appropriate.

For more detail on PBAC's view, see Section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (45), health care professionals (1) and organisations (4) via the Consumer Comments facility on the PBS website and other correspondence. The comments described a range of benefits of treatment with dabrafenib+trametinib adjuvant therapy including manageable adverse events, the ease of oral administration, and also a reduction in stress and anxiety for patients with no other adjuvant therapy options available.
- 6.3 The PBAC noted the correspondence received from Melanoma Patients Australia (MPA) supporting the listing. MPA also provided a summary of individual patient comments, describing the benefits of reduced risk of recurrence and treatment efficacy and the need for equitable access and choice of treatments. Comments via the MPA also expressed that adjuvant treatment was a worthwhile financial investment in terms of delaying or preventing recurrence at a later stage of disease with greater complications. The PBAC also noted the combined advice from Melanoma Consumers Alliance (AMCA) with the Melanoma Research Victoria Consumer Reference Group (MRV-CRG) which expressed support for the listing.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the submission. It recognised the immature survival data but noted there was a significant unmet need for adjuvant treatment of melanoma with a high risk of recurrence. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)[§] score for dabrafenib+trametinib adjuvant treatment, which was Grade A (out of C, which is the highest possible grade and restricted to new approaches to adjuvant therapy or

[§] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017.

potentially new curative treatments), based a comparison with placebo in the COMBI-AD trial.

Clinical trials

6.5 The submission was based on one head-to-head trial comparing dabrafenib+trametinib to placebo for the adjuvant treatment of patients with BRAF V600 mutation positive cutaneous melanoma after complete surgical resection, COMBI-AD (N = 870).

6.6 Details of the trial presented in the submission are provided in the table below.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/Publication title	Publication citation
COMBI-AD	COMBI-AD: A Phase III randomized double-blind study of dabrafenib (GSK2118436) in COMBination with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection.	November 2017
	Long G, Hauschild A et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma.	<i>NEJM</i> 2017; 377(19):1813-1823.
	Hauschild A, Dummer R et al. Longer Follow-Up Confirms Relapse-Free Survival Benefit With Adjuvant Dabrafenib Plus Trametinib in Patients With Resected BRAF V600-Mutant Stage III Melanoma.	<i>J Clin Oncol</i> 2018; DOI: 10.1200/JCO.18.01219.
	Long G, Hauschild A et al. Efficacy outcomes in the phase 3 COMBI-AD study of adjuvant dabrafenib (D) plus trametinib (T) versus placebo (PBO) in patients (pts) with stage III BRAF V600E/K-mutant melanoma. (Abstract).	<i>Pigment Cell and Melanoma Research</i> 2018; 31(1):182-183.
	Hauschild A, Santinami M et al. COMBI-AD: Adjuvant dabrafenib (D) plus trametinib (T) for resected stage III BRAF V600/K-mutant melanoma.	<i>Ann Oncol</i> 2017; 28(Supplement 5):631.

Source: Table 2.2-1, p39 of the submission.

6.7 The key features of the direct randomised trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ Duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Dabrafenib+trametinib vs. placebo						
COMBI-AD	870	R, DB 42 to 44 months	Low	Completely resected high risk Stage III melanoma patients ^a with positive BRAF V600E/K mutations	RFS, DMFS, OS ^b	Used

DB = double blind; DMFS = distant metastasis-free survival; OS = overall survival; R = randomised; RFS = relapse-free survival
RFS defined as time from randomisation to disease recurrence (loco-regional, distant metastases and second primary melanoma) or death from any cause.

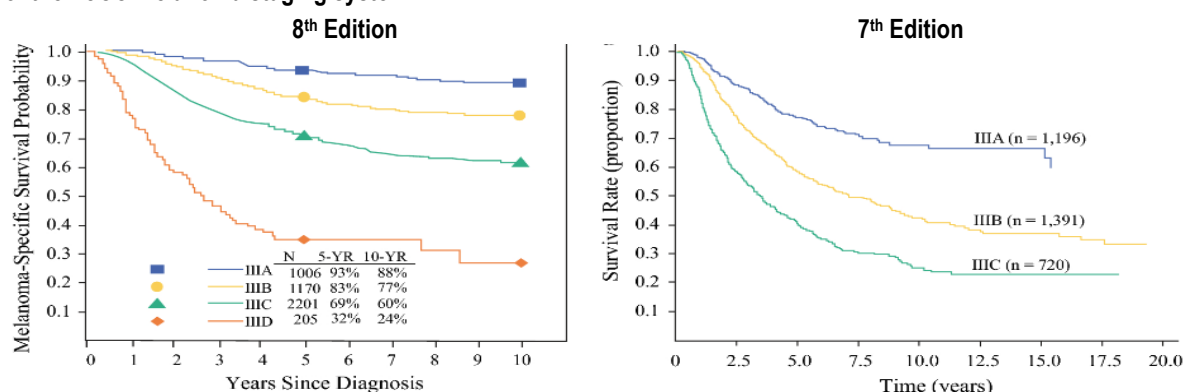
Source: Sections 2.3-2.4 of the submission

^a Stage IIIA (metastases > 1 mm), Stage IIIB and Stage IIIC, based on the 7th edition of American Joint Committee on Cancer staging manual

^b OS follow-up 33-34 months (interim analysis)

6.8 Patients in COMBI-AD were classified using the 7th edition of the AJCC melanoma staging system, which has three prognostic sub-stages, Stages IIIA, IIIB and IIIC, depending upon the extent of lymphatic involvement and the characteristics of the primary tumour. Since 2018, the 8th edition of the AJCC staging system^{**} has been used to classify melanoma patients in Australia; this subdivides patients into four prognostic sub-stages, Stages IIIA, IIIB, IIIC and IIID. The figure below presents a comparison of survival probabilities for each sub-stage of Stage III melanoma using the 7th and 8th editions of the AJCC staging system.

Figure 1: Comparison of survival probability for melanoma using the 7th (RIGHT panel) and 8th (LEFT panel) editions of the AJCC melanoma staging system



AJCC = American Joint Committee on Cancer; YR = year

Source: Gershenwald JE, Scolyer RA. Melanoma Staging: American Joint Committee on Cancer (AJCC) 8th edition and beyond. *Annals of Surgical Oncology*. 2018; 25(8): 2105-2110.

6.9 The above comparison suggested that patients in the 8th edition cohort had a more favourable survival profile across Stages IIIA, IIIB, and IIIC disease compared with patients with similar stage groupings in the 7th edition. It should be noted that the two survival curves were based on populations with substantially different prognostic profiles. Gershenwald (2018) noted that patients included in the 8th edition analyses were diagnosed since 1988, whereas the 7th edition analyses included patients

^{**} Gershenwald JE, Scolyer RA, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA: A Cancer Journal for Clinicians*. 2017; 67(6):472-92.

diagnosed in the 1960s. The better disease-specific survival from the 8th edition may be explained by the evolution of surgery, medicine, pathology and nuclear medicine. Additionally, the more recent development of post-recurrence therapies for unresectable or metastatic melanoma (e.g. PD-1 inhibitors and targeted therapies) may mean that the stage-specific survival data presented in the 8th edition were not applicable to the proposed PBS population or to the trial patients. Nonetheless, the ESC noted that Stage III disease is associated with heterogeneous outcomes; five-year melanoma-specific survival rates range from 93% for Stage IIIA disease to 32% for Stage IIID disease (8th edition), and that the distribution of patients across the subcategories in clinical practice may be different to that in the COMBI-AD trial. In particular, use of dabrafenib+trametinib in a higher proportion of lower risk Stage IIIA patients (including in patients with metastases ≤ 1 mm) would result in dabrafenib+trametinib being less cost-effective.

- 6.10 The majority of the COMBI-AD trial population, when classified using the 7th edition, had Stage IIIB or Stage IIIC disease (80% in the dabrafenib+trametinib arm and 81% in the placebo arm). A *post hoc* analysis of COMBI-AD re-staged the patients according to 8th edition^{††} – see table below – and compared this to the proportions of Stage III disease in Australian population, as reported in Haydu (2017).

Table 4: Comparison of disease stage at baseline in COMBI-AD using the 7th and 8th editions and the Australian population using the 8th edition of the AJCC melanoma staging system

	Stage at baseline – 7 th edition		Stage at baseline – 8 th edition		
	DAB+TRAM	Placebo	DAB+TRAM	Placebo	Australian population Haydu (2017) ^a
IIIA (metastases > 1 mm)	83 (19%)	71 (16%)	50 (11%)	39 (9%)	220 (5%) ^b
IIIB	169 (39%)	187 (43%)	145 (33%)	154 (36%)	2,007 (44%)
IIIC	181 (41%)	166 (38%)	217 (50%)	214 (50%)	1,709 (38%)
IIID	-	-	22 (5%)	17 (4%)	104 (23%)
III unspecified/missing	5 (1%)	8 (2%)	4 (< 1%)	8 (2%)	-

AJCC = American Joint Committee on Cancer; DAB+TRAM = dabrafenib plus trametinib

Source: Hauschild et al 2018, Haydu et al 2017

^a Included patients with Stage III disease regardless of resectable/unresectable status or BRAF mutation status

^b Included patients with Stage IIIA disease metastases ≤ and > 1 mm

- 6.11 The PBAC noted that the proportion of patients in the COMBI-AD trial with Stage IIID disease, classified using the 8th edition, was low compared to the Australian population.
- 6.12 For patients in the dabrafenib+trametinib and the placebo treatment arms of COMBI-AD who had a distant recurrence following an initial local recurrence, the distant recurrence was not counted in the RFS analysis as only the first occurrence was counted as an event. Distant relapses have a poorer prognosis compared with

^{††} Hauschild A, Dummer R, et al. Longer Follow-Up Confirms Relapse-Free Survival Benefit With Adjuvant Dabrafenib Plus Trametinib in Patients With Resected BRAF V600-Mutant Stage III Melanoma. *J Clin Oncol*. 2018;JCO1801219.

locoregional relapse. RFS data does not provide a complete picture of the adjuvant treatment benefit of dabrafenib+trametinib and is not a good surrogate for OS.

Comparative effectiveness

Adjuvant treatment

6.13 The results of RFS at data cut-off (30 June 2017) are presented below. The median duration of follow-up was 34 months for the dabrafenib+trametinib arm and 33 months for the placebo arm.

Table 5: Primary analysis of relapse-free survival at data cut-off (30 June 2017); Intention-to-treat population

	Dabrafenib+trametinib (N = 438)	Placebo (N = 432)
Relapse events ^a , n (%)	163 (37%)	247 (57%)
Local/regional recurrence ^b	61 (14%)	114 (26%)
Distant recurrence ^b	103 (24%)	133 (31%)
Second primary melanoma ^c	7 (2%)	8 (2%)
Deaths ^d , n (%)	3 (< 1%)	1 (< 1%)
Censored patients ^e , n (%)	272 (62%)	184 (43%)
Follow-up ended	43 (10%)	35 (8%)
Follow-up ongoing	229 (52%)	149 (34%)
RFS percentiles, months (95% CI)		
25th percentile	17.9 (16.6, 21.4)	5.3 (3.3, 5.6)
Median time	NE (44.5, NE)	16.6 (12.7, 22.1)
75th percentile	NE	NE
Hazard ratio vs. placebo (95% CI); p-value	0.47 (0.39, 0.58) p < 0.001	
Kaplan-Meier estimates, % (95% CI)		
1-year RFS rate	88% (85, 91)	56% (51, 61)
2-year RFS rate	67% (63, 72)	44% (40, 49)
3-year RFS rate	58% (54, 64)	39% (35, 44)

CI = confidence interval; NE = not estimable; RFS = relapse-free survival

Note: only the first occurrence is counted as an event. i.e. if a patient experienced a local recurrence first followed by a distant recurrence at a later time point, only the former one is counted as an event.

^a Relapse events (local recurrence, distant recurrence, second primary melanoma) are not mutually exclusive

^b 7 patients in each arm had both local/regional and distant recurrence observed on the same day.

^c 1 patient in the dabrafenib+trametinib arm and 1 patient in the placebo arm had both disease recurrence and secondary primary melanoma observed on the same

^d Included in relapse events

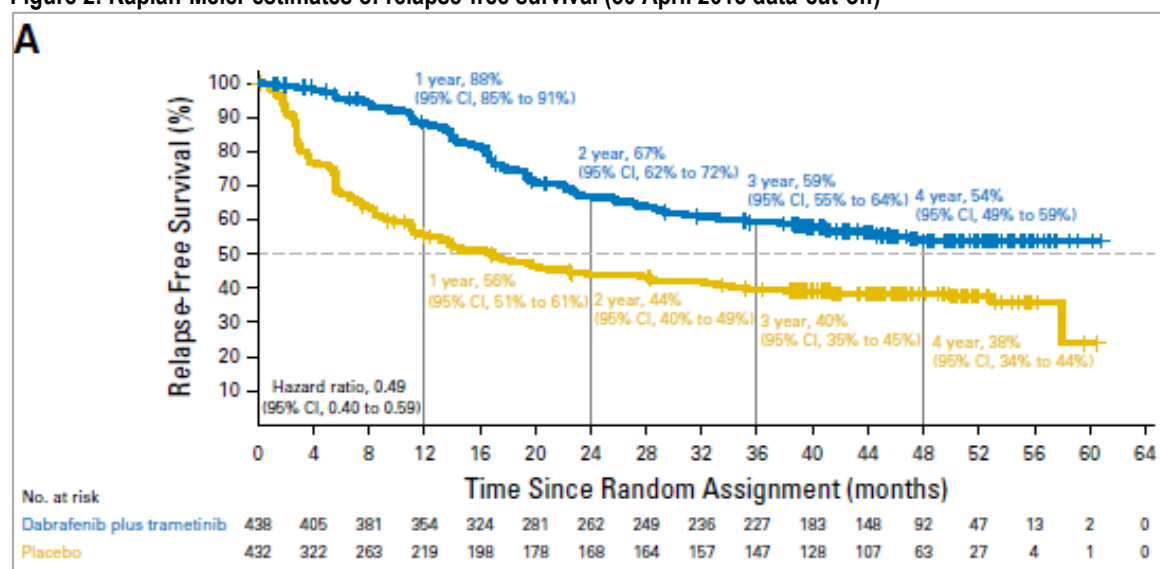
^e Patients censored with follow-up ongoing are those who were alive, did not take any anti-cancer therapy and did not withdraw from study by the time of data cut-off. Patients censored with follow-up ended are the remaining censored patients

Source: Table 2.5-1, p58 of the submission, Table 11-3, p108 of CSR of COMBI-AD trial

6.14 The risk of recurrence was significantly reduced in the patients treated with dabrafenib+trametinib compared with those treated with placebo (HR = 0.47; 95% CI: 0.39, 0.58).

6.15 The submission also presented an updated RFS analysis at a median follow-up of 44 months for the dabrafenib+trametinib arm and 42 months for the placebo arm. The updated RFS results were similar to those presented above. The Kaplan-Meier estimates for RFS from the updated analysis are presented below.

Figure 2: Kaplan-Meier estimates of relapse-free survival (30 April 2018 data-cut-off)



CI = confidence interval

Source: Figure 2.5-2, p59 of the submission

- 6.16 The Pre-Sub-Committee Response (PSCR) argued that at a median follow-up of 42 to 44 months the Kaplan-Meier RFS curves for both arms had flattened out with estimated cure rates (i.e. patients who will remain relapse-free long term) of 54% (95% CI: 49%, 59%) for dabrafenib+trametinib and 37% (95% CI: 32%, 42%) for placebo (from Hauschild, 2018). On this basis, the PSCR considered that a median time for relapse may not be reached. The ESC considered, given the immaturity of the OS data, there are currently insufficient data to conclude that dabrafenib+trametinib cures patients, as opposed to delaying recurrence.
- 6.17 Of the relapse events observed in COMBI-AD, a higher proportion in the dabrafenib+trametinib treatment arm were a distant relapse 111/174; 63.7%) compared with the placebo arm 136/253; 53.8%). Distant relapses have a poorer prognosis compared with locoregional relapse. The ESC considered this could have implications for the expected OS and noted that this difference was not accounted for in the economic model. The pre-PBAC response noted that there were few patients with relapse events in the dabrafenib+trametinib arm, and that as a proportion of all randomised patients, 25.3% of patients in the dabrafenib+trametinib arm and 31.5% of patients in the placebo arm experienced a distant relapse.
- 6.18 A publication of the COMBI-AD trial (Hauschild, 2018) reported a *post hoc* subgroup analysis of the updated RFS data conducted on the basis of baseline disease stage according to the AJCC 8th edition. The results are presented below.

Table 6: Comparison of an analysis of RFS from the COMBI-AD trial results, on the basis of baseline disease staging using 7th and 8th editions of the AJCC melanoma staging system^a

Stage III sub-stage	7 th edition		8 th edition			
	HR (95% CI)	AD at Year 3	HR (95% CI)	DAB+TRAM RFS at Year 3 (95% CI)	PBO RFS at Year 3 (95% CI)	AD at Year 3
A ^b	0.44 (0.23, 0.84) (N = 154)	18%	0.63 (0.26, 1.56) (N = 89)	84% (74% to 96%)	71% (58% to 88%)	13%
B	0.50 (0.37, 0.67) (N = 356)	19%	0.48 (0.34, 0.67) (N = 299)	64% (56% to 72%)	43% (35% to 52%)	21%
C	0.45 (0.33, 0.60) (N = 347)	20%	0.50 (0.38, 0.64) (N = 431)	52% (46% to 60%)	33% (27% to 40%)	19%
D	NA	NA	0.34 (0.14, 0.79) (N = 39)	43% (26% to 70%)	18% (6% to 49%)	25%
Missing	N = 13	–	N = 12	–	–	–

AD = absolute difference; AJCC = American Joint Committee on Cancer; CI = confidence interval; DAB+TRAM = dabrafenib+trametinib; HR = hazard ratio; NA = not applicable; PBO = placebo; RFS = relapse-free survival

^a Median follow-up of 44 months for dabrafenib+trametinib patients, 42 months for placebo patients

^b Stage A > 1 mm lymph node metastasis

Source: CSR for COMBI-AD p159; Hauschild (2018)

6.19 The ESC noted in the placebo arm and using the 8th edition of the staging manual, the RFS rate at 3 years varied from 71% for Stage IIIA to 18% for Stage IIID. Dabrafenib+trametinib improved RFS, according to the point estimate, across all 8th edition staging subgroups, compared with placebo. The results were not statistically significant for Stage IIIA; however, the subgroup was not sufficiently powered to detect a true difference.

6.20 The results of DMFS at data cut-off (30 June 2017) are presented below.

Table 7: Secondary analysis of DMFS at data cut-off (30 June 2017); ITT population

	Dabrafenib+trametinib (N = 438)	Placebo (N = 432)
Relapse events, n (%)	106 (24%)	150 (35%)
Deaths (event), n (%)	4 (< 1%)	2 (< 1%)
Censored patients, n (%)	328 (75%)	280 (65%)
Follow-up ended	99 (23%)	131 (30%)
Follow-up ongoing	229 (52%)	149 (34%)
DMFS percentiles, months (95% CI)		
25th percentile	27.4 (21.9, 39.5)	8.3 (5.7, 12.0)
Median time	NE	NE (41.2, NE)
75th percentile	NE	NE
Hazard ratio vs. placebo (95% CI); p-value	0.51 (0.40, 0.65) p < 0.001	
Kaplan-Meier estimates, % (95% CI)		
1-year DMFS rate	91% (88, 94)	70% (66, 75)
2-year DMFS rate	77% (73, 82)	60% (55, 66)
3-year DMFS rate	71% (66, 76)	57% (52, 63)

CI = confidence interval, DMFS = distant metastases-free survival, NE = not estimable

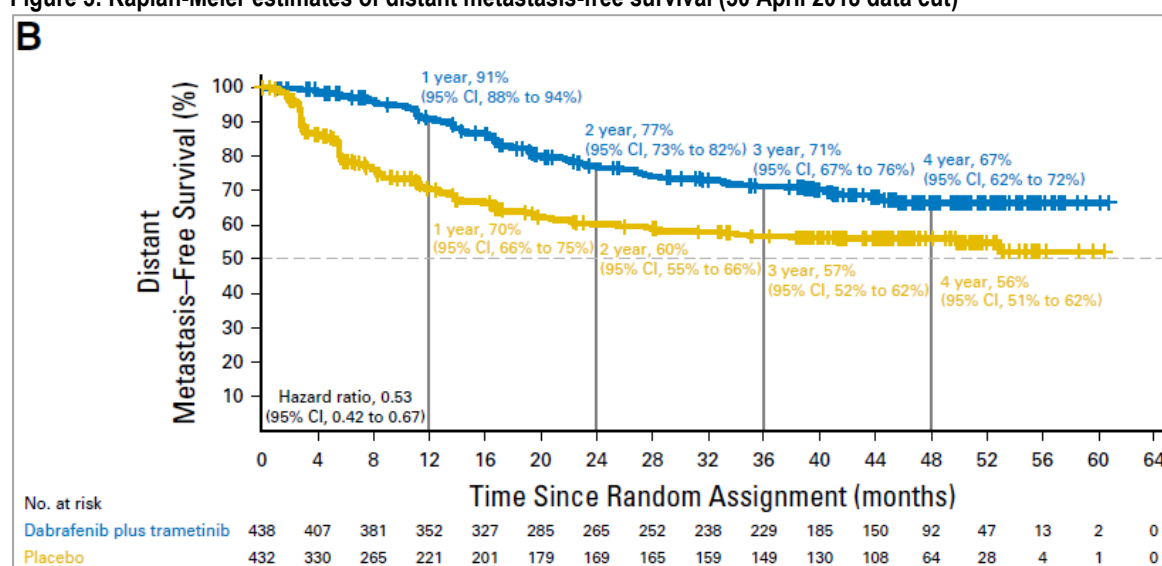
Source: Table 2.5.4 of the submission (COMBI-AD CSR, Section 11.2.2.3 Table 14.2-2.2 pdf p 289, Table 14.2-2.12 pdf p 304-305)

6.21 In the updated analysis (30 April 2018 data cut), the efficacy of dabrafenib+trametinib was maintained, with the risk of developing distant metastasis statistically significantly reduced with dabrafenib+trametinib compared with placebo (HR = 0.53; 95% CI: 0.42,

0.67). The median DMFS was not reached in either treatment group due to low event rates. The ESC advised that DMFS may be a more reliable predictor of OS than RFS, although subject to similar uncertainty in the absence of mature OS data.

6.22 The Kaplan-Meier estimates of the DMFS from the updated analysis are presented below.

Figure 3: Kaplan-Meier estimates of distant metastasis-free survival (30 April 2018 data cut)



CI = confidence interval

Source: Figure 2.5-5 of the submission (Hauschild et al, 2018)

6.23 The OS results, from the 30 June 2017 data cut for the intention-to-treat population in COMBI-AD, are presented below.

Table 8: Interim analysis of OS at 30 June 2017 data cut; Intention-to-treat population

COMBI-AD	Dabrafenib+trametinib (N = 438)	Placebo (N = 432)
Deaths, n (%)	60 (14%)	93 (22%)
Median OS, months (95% CI)	NR	NR
Hazard ratio vs. placebo (95% CI); p-value	0.57 (0.42, 0.79) p = 0.0006	
Kaplan-Meier estimates, % (95% CI)		
1-year OS rate	97% (95, 99)	94% (92, 96)
2-year OS rate	91% (88, 94)	83% (79, 86)
3-year OS rate	86% (82, 89)	77% (72, 81)

CI = confidence interval; NE = not estimable; OS = overall survival

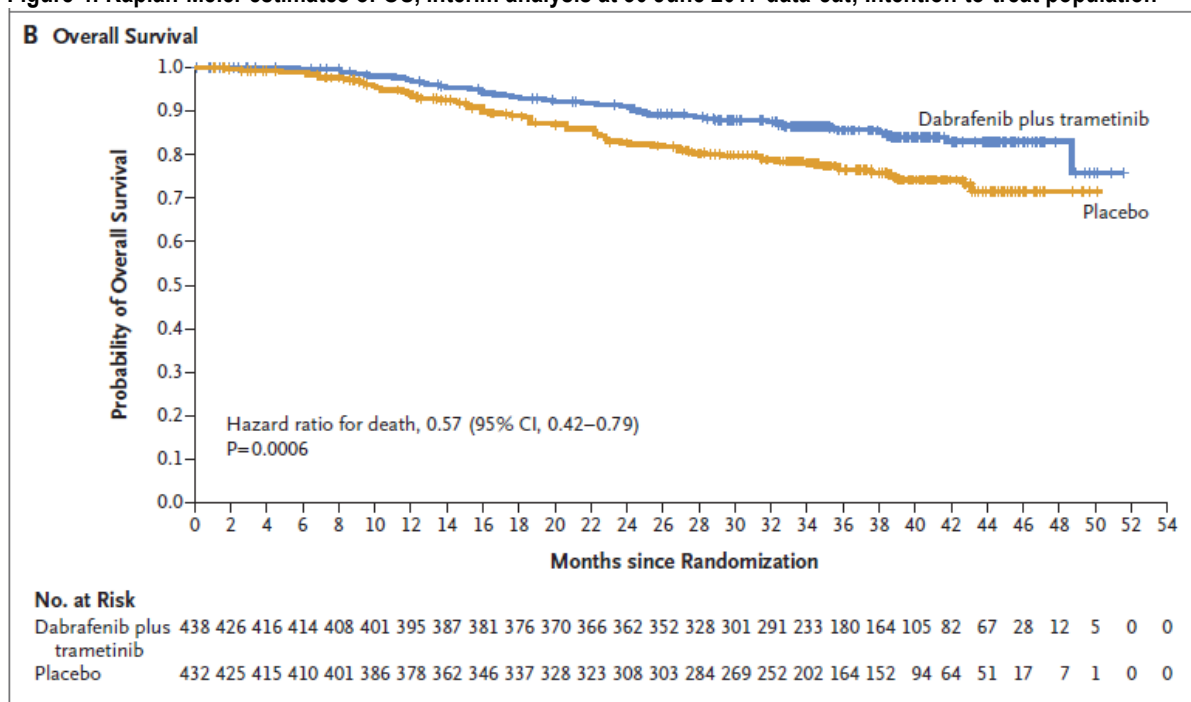
Source: Table 2.5-3, p61 of the submission

6.24 A total of 153 patients had died; 60 (14%) in the dabrafenib+trametinib group and 93 (22%) in the placebo group. The total deaths that occurred represented 26% of the 597 deaths required for the final OS analysis. The risk of death was reduced in patients treated with dabrafenib+trametinib compared with those treated with placebo at a median follow up of 34 months dabrafenib+trametinib and 33 months placebo (HR = 0.57; 95% CI: 0.42, 0.79, p = 0.0006). Although the HR was statistically significant, it did not meet the pre-specified threshold for the first interim analysis (in place because of multiple testing considerations). The significance threshold for

the first interim analysis was $p = 0.000019$. As median OS was not reached in either arm, the magnitude of any OS benefit cannot be reliably determined.

6.25 The Kaplan-Meier plots for OS are presented in the figure below.

Figure 4: Kaplan-Meier estimates of OS, interim analysis at 30 June 2017 data-cut; Intention-to-treat population



CI = confidence interval

Source: Figure 2.5-3, p61 of the submission

6.26 The results of utility scores from the EQ-5D questionnaire in COMBI-AD are presented in the table below.

Table 9: Quality of Life EuroQoL-5 dimension (EQ-5D) utility scores from COMBI-AD trial

	Dabrafenib + trametinib (N = 438)		Placebo (N = 432)		Mean difference vs placebo (95% CI)
	Mean (SD)	Change from baseline, Adjusted mean (SE)	Mean (SD)	Change from baseline, Adjusted mean (SE)	
Baseline	N = [REDACTED] [REDACTED] ([REDACTED])	-	N = [REDACTED] [REDACTED] ([REDACTED])	-	-
Month 3	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 6	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 9	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 12	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 18	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 24	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 30	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 36	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 42	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 48	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	N = [REDACTED] [REDACTED] ([REDACTED])	n = [REDACTED] [REDACTED] ([REDACTED])	([REDACTED], [REDACTED])
Month 54	N = [REDACTED] [REDACTED] ([REDACTED])	[REDACTED]	N = [REDACTED] [REDACTED] ([REDACTED])	[REDACTED]	-

CI = confidence interval; NR = not reported; N = represents the corresponding number of subjects with non-missing utility score at each time point; n = represents the corresponding number of subjects with all available covariates at each time point; SE = standard error

Note: The analysis method was analysis of covariance adjusted for baseline score using mixed-model repeated measures with time, treatment, and baseline score by time interaction, and treatment by time interaction as fixed effects. Time was treated as the repeated variable within subject. An unstructured covariance matrix was used. Time points with n greater than or equal to 20 were included in the model.

Source: Table 2.5-6, p66 of the submission

6.27 Quality of life (QoL) data were collected from the intention-to-treat population. The ESC noted the high dropout rate in both arms (N = 429 and 422 for the intervention and placebo arms respectively at baseline and N = 42 and 31 for each arm at Month 48), which was unexplained in the submission. The ESC advised that patients who had a better overall QoL might have been more likely to complete the QoL questionnaire than those who did not feel well, which may have resulted in an overestimated utility value for each health state. In addition, the ESC noted that the first time point for assessment of QoL post-baseline was Month 3. As adverse events often occur early in treatment, the disutility associated with dabrafenib+trametinib might not have been fully captured in the trial-based QoL data.

Retreatment

6.28 It has been reported that in clinical practice, the combination of BRAF and MEK inhibitors is highly active for BRAF mutant melanoma patients, but the duration of

response is limited due to the development of an acquired and adaptive resistance mechanism^{††}. Tumour heterogeneity is a major driver of resistance in melanoma. Therefore, more evidence is required to confirm the benefit of retreatment with dabrafenib±trametinib for unresectable or Stage IV disease after adjuvant treatment with this combination therapy. The PSCR argued that in COMBI-AD only 5% of patients relapsed while on treatment, therefore acquired resistance with adjuvant dabrafenib+trametinib was not supported by the evidence. It was also argued that there was a high clinical need for patients who progress following completion of adjuvant therapy.

- 6.29 The ESC noted that COMBI-AD was not designed to test the efficacy and safety of repeated exposure to dabrafenib+trametinib after relapse. However, a *post hoc* analysis of evaluable data was presented. The choice of post-recurrence therapy (see table below) was at the discretion of the treating physician, and it was unclear what criteria were considered when choosing a particular therapy.

Table 10: Targeted therapies use as post-relapse therapies (based on population who had relapsed)

COMBI-AD	Dabrafenib+trametinib (N = 163)	Placebo (N = 247)
Any post-relapse anti-cancer therapy, n (%)		
Yes	■ (■%)	■ (■%)
No	■ (■%)	■ (■%)
Type of post-relapse anti-cancer therapy, n (%)		
Any systemic anti-cancer therapy	■ (■%)	■ (■%)
PD-1 inhibitor	■ (■%)	■ (■%)
PD-L1 inhibitor	■ (■%)	■ (■%)
Chemotherapy	■ (■%)	■ (■%)
Small molecule targeted therapy (any)	■ (■%)	■ (■%)
Any BRAF V600 inhibitor	■ (■%)	■ (■%)
Dabrafenib	■ (■%)	■ (■%)
Vemurafenib	■ (■%)	■ (■%)
Encorafenib	■ (■%)	■ (■%)
Any MEK inhibitor	■ (■%)	■ (■%)
Trametinib	■ (■%)	■ (■%)
Cobimetinib	■ (■%)	■ (■%)
Binimetinib	■ (■%)	■ (■%)

MEK = mitogen-activated extracellular signal regulated kinase; N = total patients in the group

Source: Table 2.6-2, p73 of the submission

- 6.30 The best response to targeted therapies after relapse was evaluable in ■ patients who had received dabrafenib+trametinib and in ■ patients who had received placebo – see table below. This analysis was subject to selection bias.

^{††} Manzano JL, Layos L, et al. Resistant mechanisms to BRAF inhibitors in melanoma. *Ann Transl Med.* 2016;4(12):237.

Table 11: Response of relapsed patients in COMBI-AD re-treated with any targeted therapy

COMBI-AD	Dabrafenib+trametinib	Placebo
Evaluable for response, n	■ ^a	■ ^a
Overall response (complete + partial response), n (%)	■ (■%)	■ (■%)
Disease control rate ^b , n (%)	■ (■%)	■ (■%)
Complete response, n (%)	■ (■%)	■ (■%)
Partial response, n (%)	■ (■%)	■ (■%)
Stable disease, n (%)	■ (■%)	■ (■%)
Disease progression, n (%)	■ (■%)	■ (■%)

^a Relapsed patients who received any targeted therapy and were evaluable for response (n = ■ in the dabrafenib + trametinib arm and n = ■ in the placebo arm were non-evaluable for response due to local relapses followed by complete resection or responses were non-applicable or unknown).

^b Calculated from the sum of patients with complete response, partial response and stable disease

Note: Data cut-off June 2017

Source: Table 2.6-3, p74 of the submission

Comparative harms

6.31 The results of adverse events from COMBI-AD are summarised below. Patients treated with dabrafenib+trametinib were nearly three time more likely to experience Grade 3 or 4 adverse events, nine times more likely to have adverse events leading to treatment discontinuation, and nearly seven times more likely to experience serious adverse events related to study treatment, compared with those treated with placebo. The safety risks with dabrafenib+trametinib were significantly higher than placebo for all adverse event outcomes except fatal serious adverse events. The ESC noted dabrafenib+trametinib was commonly associated with fever, fatigue and gastrointestinal events.

Table 12: Summary of adverse events for COMBI-AD trial; Safety population

Adverse events, n (%)	DAB+TRAM (N = 435)	Placebo (N = 432)	RR (95% CI) ^a	RD (95% CI) ^a
Any AE (all grades)	422 (97%)	380 (88%)	1.10 (1.06, 1.15)	0.09 (0.06, 0.13)
Grade 3 or 4	180 (41%)	61 (14%)	2.93 (2.26, 3.79)	0.27 (0.22, 0.33)
AEs related to study treatment	398 (91%)	272 (63%)	1.45 (1.34, 1.57)	0.29 (0.23, 0.34)
AEs leading to permanent discontinuation of study treatment	114 (26%)	12 (3%)	9.43 (5.28, 16.85)	0.23 (0.19, 0.28)
AEs leading to dose reduction	167 (38%)	11 (3%)	15.08 (8.31, 27.35)	0.36 (0.31, 0.41)
AEs leading to interruption	289 (66%)	65 (15%)	4.42 (3.49, 5.58)	0.51 (0.46, 0.57)
Any SAE	155 (36%)	44 (10%)	3.50 (2.57, 4.76)	0.25 (0.20, 0.31)
SAEs related to study treatment	117 (27%)	17 (4%)	6.83 (4.18, 11.17)	0.23 (0.18, 0.28)
Fatal SAEs	1 (< 1%)	0	2.98 (0.12, 72.93)	0.00 (-0.00, 0.01)
Any Drug-related AEs (Grade ≥ 3)	136 (31%)	21 (5%)	6.43 (4.14, 9.98)	0.26 (0.22, 0.31)

AE = adverse event; CI = confidence interval; DAB+TRAM = dabrafenib+trametinib; RD = risk difference; RR = relative risk; SAE = serious adverse event

^a Calculated for the purpose of the submission using Review Manager

Source: Table 2.5-8, p69 & Table 2.5-9, p71 of the submission

6.32 A Periodic Safety Update Report (PSUR) for trametinib reported that neutropenia was included in the trametinib risk management plan as an important identified risk when trametinib was used in combination with dabrafenib only. In COMBI-AD, neutropenia events were observed in 51 (12%) patients in the dabrafenib+trametinib arm, and 6 (1%) patients in the placebo arm. In the dabrafenib+trametinib arm, 21/51 patients

had Grade 3 neutropenia events; all neutropenia events in the placebo arm were Grade 1 or 2.

Benefits/harms

6.33 A summary of the comparative benefits and harms for dabrafenib+trametinib versus placebo is presented in the table below.

Table 13: Summary of comparative benefits and harms for dabrafenib+trametinib and placebo from COMBI-AD^a

Benefits						
	DAB+TRAM	Placebo	Absolute difference	HR (98.4% CI)		
Relapse-free survival						
Relapse events, n/N (%)	163/438 (37%)	247/432 (57%)	-	0.47 (0.39, 0.58)		
Median RFS, months (95% CI)	NR (44.5, NR)	16.6 (12.7, 22.1)	-			
3-year RFS rate, %	58%	39%	19%			
Distant metastases-free survival						
Events, n/N (%)	106/438 (24%)	150/423 (35%)	-	0.51 (0.40, 0.65)		
Median DMFS, months (95% CI)	NE	NE (41.2, NE)	-			
3-year DMFS rate, %	71%	57%	14%			
Overall survival						
Death, n/N (%)	60/438 (14%)	93/432 (22%)	-	0.57 (0.42, 0.79)		
Median OS, months (95% CI)	NR	NR	-			
3-year OS rate, %	86%	77%	9%			
Harms						
	DAB+TRAM	Placebo	Relative risk (95% CI)	Event rate/100 patients		RD (95% CI)
				DAB+TRAM	Placebo	
Grade 3-4 AEs	180/435	61/432	2.93 (2.26, 3.79)	41	14	0.27 (0.22, 0.33)
AEs leading to treatment discontinuation	114/435	12/432	9.43 (5.28, 16.85)	26	3	0.23 (0.19, 0.28)
Serious AEs	155/435	44/432	3.50 (2.57, 4.76)	36	10	0.25 (0.20, 0.31)

AE = adverse event; CI = confidence interval; DAB+TRAM = dabrafenib+trametinib; DMFS = distant metastases free survival; HR = hazard ratio; NR = not reached; OS = overall survival; RD = risk difference; RFS = relapse-free survival

^a Median duration of follow-up 34 months dabrafenib+trametinib and 33 months placebo

Source: Table 2.5-1, p58, Table 2.5-3, p61, Table 2.5-4, p63, Table 2.5-8, p69 & Table 2.5-9, p71 of the submission

6.34 On the basis of evidence presented by the submission, for every 100 patients treated with dabrafenib+trametinib in comparison to placebo:

- Approximately 19 fewer patients would have a relapse at 3 years;
- Approximately 14 fewer patients would have a distant relapse at 3 years;
- Approximately 9 more patients may remain alive at 3 years (although this result did not meet the pre-specified threshold for significance) ;
- Approximately 27 additional patients would experience a Grade 3-4 adverse event;
- Approximately 23 additional patients would experience an adverse event leading to treatment discontinuation; and
- Approximately 25 additional patients would experience a serious adverse event.

- 6.35 For patients with Stage IIIA melanoma with lymph node metastasis ≤ 1 mm (not included in the COMBI-AD trial), the benefit to risk ratio for the use of dabrafenib+trametinib was unknown.

Clinical claim

- 6.36 The submission described dabrafenib+trametinib as superior in terms of RFS and OS, but inferior in terms of safety to placebo.
- 6.37 The submission's claim that dabrafenib+trametinib was superior to placebo in terms of RFS for adjuvant treatment of completely resected Stage III, BRAF V600 mutation positive melanoma, was reasonable, based on the evidence presented in COMBI-AD. A RFS benefit was apparent for the intervention arm in the key COMBI-AD trial, although the magnitude was uncertain as the median RFS had not yet been reached for the intervention arm.
- 6.38 The ESC considered the magnitude of RFS benefit for patients with Stage IIIA (metastasis > 1 mm) was uncertain due to the small proportion of patients with this sub-stage of disease recruited into the trial. The ESC noted that the effectiveness of dabrafenib+trametinib in patients with Stage IIIA (metastasis ≤ 1 mm) was unknown as these patients were not included in the trial population.
- 6.39 Due to the immaturity of the OS data (only a small number of deaths, (n=153, 26%) had occurred at the first interim analysis cut-off) the magnitude of the effectiveness of dabrafenib+trametinib remained uncertain. A second interim analysis of OS will be available by [REDACTED], when approximately 50% of OS events are expected to have occurred. The ESC noted, if recommended, the PBAC may wish to consider whether the cost-effectiveness of dabrafenib+trametinib should be reviewed when additional OS data are available.
- 6.40 The incidence of Grade 3 or 4 adverse events, serious adverse events and discontinuation due to adverse events were all higher for dabrafenib+trametinib compared to placebo. The adverse events for dabrafenib+trametinib in the melanoma adjuvant setting were consistent with those previously observed in the unresectable or metastatic melanoma setting.
- 6.41 The PBAC considered that the claim of superior comparative effectiveness was reasonable based on the RFS data for patients with Stage IIIB, IIIC and IIID disease. However, the immature OS data meant that the magnitude of the clinical benefit of adjuvant dabrafenib+trametinib therapy was uncertain. The PBAC considered that the incremental effectiveness of dabrafenib+trametinib in Stage IIIA patients was particularly uncertain (see paragraph 2.8), but it was likely to be modest (see paragraphs 6.8 to 6.10 and Figure 1).
- 6.42 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.43 The submission presented a modelled economic evaluation, based on the COMBI-AD trial. The type of economic evaluation presented was a cost-effectiveness analysis and

a cost-utility analysis, measuring outcomes in terms of life-years (LY) gained and quality-adjusted life years (QALY) gained, respectively. The key components of the economic evaluation are summarised below.

Table 14: Summary of model structure and rationale

Component	Summary
Time horizon	48 months in the model versus 52 months ^a in the COMBI-AD clinical trial
Outcomes	LYs and QALYs
Methods used to generate results	Cohort analysis using a partitioned survival approach
Health states	Three health states: RFS, recurrent disease and death
Cycle length	1 month
Health state allocation	The proportion of patients in each health state was determined from the RFS and OS curves. The Kaplan-Meier estimates for RFS and OS from COMBI-AD were applied to the economic model up to the extrapolation time point. Thereafter, parametric distributions fitted to the observed Kaplan-Meier survival estimates were used to extrapolate RFS and OS beyond the follow-up of COMBI-AD to the end of the time horizon of the model.

LY = life year; OS = overall survival; QALY = quality-adjusted life year; RFS = relapse-free survival

^a The median follow-up in COMBI-AD was 42-44 months. 52 months corresponds the latest available OS data for dabrafenib+trametinib and placebo from COMBI-AD.

Source: Table 3.1-1, p95 of the submission.

- 6.44 The trial data did not provide a reliable basis for extrapolation as median RFS was not reached in the dabrafenib+trametinib arm and median OS was not reached in either arm. The data were particularly unreliable for OS, as only 14% of patients in the dabrafenib+trametinib arm and 22% of patients in the placebo arm died during the trial observation period.
- 6.45 The ESC advised that the extent of extrapolation required with the use of a partitioned survival model rendered the results of the economic analysis highly uncertain. In addition, interpretation of the model results was hindered because recurrence events, including treatment and outcomes for each of these events, were not tracked separately. A Markov model would allow for the use of both observed data and external evidence to estimate the implications of a recurrence event, as traditionally used to evaluate therapies in the adjuvant setting. Substantial uncertainty in the cost-effectiveness ratios would remain due to immature OS data, but a Markov model would facilitate more detailed investigation of the effects of specific components of the pathway, e.g. transitions from local to metastatic recurrence, from metastatic recurrence to dead, and background mortality in the recurrence-free and local recurrence states.
- 6.46 The model included three health states: RFS, recurrent disease and death. A similar three-health state model structure was used in the July 2018 submission of nivolumab for the adjuvant treatment of completely resected Stages III and IV melanoma, over which the PBAC raised a number of concerns (paragraph 7.6, Nivolumab Public Summary Document (PSD), July 2018). Like the nivolumab model, the recurrence after adjuvant treatment health state could consist of a heterogeneous population (e.g. recurrence with local and/or distant metastases) with different final health outcomes. In addition, the application of static costs and utilities to each health state in the model may not accurately reflect the outcomes of patients treated in the adjuvant setting

over the ■ year time horizon of the model. The ESC noted the data presented in the PSCR which suggested a higher proportion of relapse events were due to distant metastases in the dabrafenib+trametinib arm of COMBI-AD (62%) compared with the placebo arm (53%), and that this difference was not accounted for with a three health state model. The pre-PBAC response stated that as the prognosis for patients with distant metastases is worse than for those with locoregional metastases, the early parts of the Kaplan-Meier OS curves are likely to represent deaths due to distant metastases. The pre-PBAC response agreed that the modelled OS for both treatment arms may be biased towards the survival for patients with distant metastases.

- 6.47 The population in the model was assumed to be the same as that in the key trial, COMBI-AD, as the trial data were used as the basis for modelling the RFS and OS benefits associated with adjuvant dabrafenib+trametinib compared with observation, without any adjustment. The submission did not adequately address the applicability of the trial population to the proposed PBS population in terms of age and disease stage.
- 6.48 The mean patient age in COMBI-AD (50.4 years), and hence the economic model was considerably younger than that reported in the Cancer in Australia 2017 Report^{§§} for newly diagnosed melanoma, regardless of disease stage (57.7 to 63.0 years). Although the economic model allowed variation of the age input, the variation only affected the age-related background mortality. Given the increasing competing risk of death from other causes in patients with advanced age, the application of a survival result from the younger patients in COMBI-AD to older patients was likely to favour dabrafenib+trametinib. The PSCR stated that Menzies et al (2012) showed BRAF mutation status to be associated with significantly younger age at diagnosis of first distant metastasis compared with BRAF wild-type melanoma (mean, 53.9 versus 62.7 years respectively). In addition, a pre-defined sub-group analysis of COMBI-AD RFS data by age (< 65 years and ≥ 65 years) showed that a meaningful and consistent clinical benefit across both age groups. The ESC considered the mean age of the trial population would be broadly representative of the proposed PBS population.
- 6.49 As presented in Table 4, approximately 18% of patients in the COMBI-AD trial had Stage IIIA (with > 1 mm metastasis) melanoma, as defined by the 7th edition of the AJCC staging system, and approximately 10% of patients had Stage IIIA (with > 1 mm metastasis) melanoma, as defined by the 8th edition. Patients with less severe Stage IIIA (with ≤ 1 mm metastasis) were not recruited for the trial. The PBAC foreshadowed a listing in patients with Stage IIIB, IIIC and IIID disease to be appropriate, although it was noted that the cost-effectiveness was assessed in patients with Stage IIIA to IIID disease; however, only 10% of trial patients had Stage IIIA disease. It was further noted that patients with Stage IIID disease may have been underrepresented given the low proportion of such patients in the COMBI-AD trial versus the Australian population (Table 4).

^{§§} <https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2017/contents/table-of-contents>

6.50 The key drivers of the model are summarised below.

Table 15: Key drivers of the model

Description	Method/Value	Impact
Extrapolation of RFS and OS	The submission modelled an ongoing survival benefit associated with dabrafenib+trametinib compared with observation beyond the 52-month ^a trial period. The model assumes an ongoing survival benefit in excess of [REDACTED] after discontinuation of adjuvant treatment.	High, favours dabrafenib+trametinib
Duration of adjuvant dabrafenib+trametinib	Duration of the dabrafenib+trametinib combination therapy was based on the modelled RFS within the first year of the model.	Moderate, favours observation

OS = overall survival; RFS = relapse-free survival

Source: Table compiled during the evaluation, based on information provided in Section 3 of the submission

^a The median follow-up in COMBI-AD was 42-44 months. 52 months corresponds the latest available OS data for dabrafenib+trametinib and placebo from COMBI-AD.

- 6.51 In the economic evaluation, trial-based RFS data were applied to the model for up to [REDACTED] months and OS data were applied for up to [REDACTED] months. Thereafter, extrapolation was performed by fitting a parametric distribution to the RFS and OS estimates observed within the clinical trial period. Based on goodness of fit statistics and visual inspection, a dependent generalised gamma function, which incorporated a time-constant treatment effect associated with dabrafenib+trametinib, was selected for both RFS and OS extrapolation in the base case. Figure 5 illustrates a comparison of the COMBI-AD trial data with the modelled survival curves.
- 6.52 Both RFS and OS curves were extrapolated using dependent parametric models (i.e. a single parametric function with a covariate for dabrafenib+trametinib). This choice was informed by an assumption of proportional hazards. The ESC advised that this was not reasonable over the [REDACTED] year time horizon of the model. The ESC noted this resulted in large differences in RFS and OS out to [REDACTED] years ([REDACTED]% difference in proportion alive and [REDACTED]% difference in RFS at [REDACTED] years) and a gain in undiscounted overall survival of [REDACTED] years which seemed implausibly large. The ESC further noted that the ICER was sensitive to changes in convergence of the curves (see Table 17), with convergence at [REDACTED] years increasing the ICER to \$105,000/QALY to \$200,000/QALY from the base case of \$15,000/QALY to \$45,000/QALY.
- 6.53 The ESC also noted that the modelled RFS curves favoured dabrafenib+trametinib with the dabrafenib+trametinib modelled curve overestimating RFS years and the placebo modelled curve underestimating RFS compared with the Kaplan-Meier curves from approximately 2 years. The ESC further noted the large variation in the estimated RFS and OS depending on the function used, despite similar goodness of fit against the clinical trial data using graphical inspection of fit, Akaike information criterion (AIC), and Bayesian information criterion (BIC).

Figure 5: Kaplan Meier and modelled curves for RFS and OS



KM = Kaplan-Meier; OS = overall survival; RFS = relapse-free survival

Source: Figure constructed during the evaluation, based on the "Dabrafenib and trametinib economic evaluation Nov 2018" excel workbook

Note: median follow up of 42 months for RFS, 33-34 months for OS.

- 6.54 The time horizon of the base case economic model was considerably longer than the maximum duration of follow-up in the key trial (■■■ years versus 52 months/4.3 years). The ESC noted that although it may be reasonable to apply a time horizon of sufficient duration to capture differences in costs and health outcomes of scenarios with and without the availability of adjuvant dabrafenib+trametinib, an incremental cost-effectiveness ratio (ICER) that is reliant on downstream costs and outcomes far beyond the follow-up duration of the clinical trial is inherently uncertain. Given the extrapolations applied, the ■■■-year time horizon favoured dabrafenib+trametinib.
- 6.55 The PSCR argued that the ■■■ year time horizon was clinically appropriate as treatment of all patients with Stage III melanoma following complete surgical resection is curative in intent, and thus a proportion of patients who are treated with either dabrafenib+trametinib or standard care will remain free of disease recurrence for the remainder of their lives. Furthermore, it argued that the ICER stabilises around ■■■ years and remains reasonably constant and below \$15,000 to \$45,000 per QALY until the end of the ■■■-year time horizon, and that any bias favouring dabrafenib+trametinib is therefore minimal. The ESC noted that approximately one-third of the total incremental LYs (■■■ out of ■■■) and QALYs (■■■ out of ■■■) gained over the ■■■ year time horizon were gained beyond ■■■ years. The ESC further noted that the ICER stabilises due to the difference in RFS reducing overtime which resulted in reduced cost offsets for recurrence treatments, i.e. as the time horizon increases from ■■■ to ■■■ years the incremental QALYs increase and the incremental costs decrease. The PBAC, noting the immature OS trial data, considered that a time horizon of ■■■ years would be more reasonable.

- 6.56 The daily dose reported in the COMBI-AD trial was used in calculating the drug cost for dabrafenib+trametinib in the model, without taking into account any drug wastage. With regard to the treatment duration, the submission assumed that patients would stay on adjuvant dabrafenib+trametinib therapy for 12 months or until disease progression. This resulted in an overestimation of the treatment duration and, thus, the drug acquisition costs. The RFS in Year 1 (■■■■ months) was longer than the mean treatment duration reported by COMBI-AD (8.2-8.3 months). The ESC noted the shorter mean treatment duration reflected the relatively large proportion of patients who discontinued treatment due to an adverse event (26%).
- 6.57 COMBI-AD data on subsequent anti-cancer treatments following disease progression were used in the economic evaluation. The treatment regimen and duration of therapy for post-recurrence treatments were sourced from 10% PBS sample analysis, product information and/or clinical practice guidelines. Overall, the pattern of use of post-recurrence therapies in the COMBI-AD trial appeared to reflect the assumed clinical practice (e.g. higher use of post-recurrence immunotherapy in the dabrafenib+trametinib arm and higher use of targeted therapy for treatment of unresectable or metastatic melanoma in the comparator observation arm). Pembrolizumab, nivolumab and ipilimumab in the unresectable or metastatic setting are listed under SPA and/or Risk-Sharing Arrangement (RSA). The published prices, therefore, are unlikely to reflect effective pricing. Sensitivity analysis presented in the submission showed that the base case ICER was not sensitive to the cost of these medicines. The PBAC noted for scenarios in which the RFS and OS curves were converged that the ICER was moderately sensitive to cost of medicines for the treatment of recurrent disease.
- 6.58 Utilities applied to the economic model were derived from COMBI-AD. As commented previously (see paragraph 6.27), the disutility associated with treatment-related AEs might not be captured in the clinical trial given the late first post-treatment QoL assessment (Month 3). This, however, was unlikely to have a large impact on the ICER due to the short on-treatment period versus the overall model time horizon (< 1 year versus ■■■■ years). The utility weight of the recurrent disease state (■■■■-■■■■) was an apparent overestimate, based on the utility values reported in other relevant economic evaluations. This overestimate favoured the observation arm, because of the longer duration of recurrent disease for patients in the observation arm and the slightly higher utility value for these patients compared with patients in the dabrafenib+trametinib group (■■■■ vs ■■■■). Moreover, given the dropout rate for the collection of QoL measures as reported in Table 9, it was unclear what number of patients had informed the utility values used in the model for the recurrent disease states. Sensitivity analyses presented in the submission showed that the base case ICER was not sensitive to the change in the utility input. The PBAC noted for scenarios in which the RFS and OS curves were converged that the ICER was moderately sensitive to the utility inputs. Overall, the ESC considered the utility values used in the model were conservative. The PBAC noted the small utility gains assumed for avoiding recurrence and considered that these were likely underestimated in the model.

6.59 The results of the economic model are summarised in Table 16. The pre-PBAC response provided an updated base case analysis to address the uncertainty associated with the assumption of continued benefit of dabrafenib+trametinib beyond the time horizon of COMBI-AD and other issues identified by ESC. The model was revised by:

- Converging the RFS and OS curves from ■ to ■ years;
- Using the dose regimen for dabrafenib+trametinib recommended in the Product Information and the mean duration of treatment from the COMBI-AD trial; and
- Reducing the proposed price (at the ex-manufacturer level) for dabrafenib and trametinib by ■%.

Table 16: Results of the stepped economic evaluation

Step	Dabrafenib+trametinib	Observation	Increment
Step 1: trial-based, time horizon of 52 months, cost for adjuvant therapy only			
Costs	\$ ■	\$ ■	\$ ■
LYs gained	■	■	■
Incremental cost/extra LY gained			\$ ■
Step 2: extrapolation of model duration to ■ years			
Costs	\$ ■	\$ ■	\$ ■
LYs gained	■	■	■
Incremental cost/extra LY gained			\$ ■
Step 3: including all resource use costs			
Costs	\$ ■	\$ ■	\$ ■
LYs gained	■	■	■
Incremental cost/extra LY gained			\$ ■
Step 4: transformation from LY gained to QALY gained			
Costs	\$ ■	\$ ■	\$ ■
QALYs gained	■	■	■
Incremental cost/extra QALY gained			\$ ■
Pre-PBAC response cost/extra QALY gained			\$ ■

LY = life-year; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life-year

Source: Table 3.8-1, p177 of the submission

6.60 The above table indicated that the extrapolation from trial observation period to ■ years had a substantial impact on the final result of the economic model. The modelled continuous and more favourable survival associated with adjuvant dabrafenib+trametinib over the time horizon was optimistic.

6.61 Overall, the ESC considered that the ICER was likely to be underestimated due to the assumed ongoing RFS and OS survival benefit associated with dabrafenib+trametinib. In addition, the model structure did not allow the cost and consequences of local/regional versus distant relapse to be assessed.

6.62 Key sensitivity analyses are presented in Table 17.

Table 17: Results of key sensitivity analyses

	Costs			Outcomes			ICER
	DAB+TRAM	OBS	Increment	DAB+TRAM	OBS	Increment	
Base case	\$██████	\$██████	\$██████	8.97	7.72	1.25	\$██████
Convergence of survival curves (base case: no)							
RFS and OS start to converge at Year █, converge at Year █ ^a	\$██████	\$██████	\$██████	████	████	████	\$██████
RFS and OS start to converge at Year █, converge at Year █ ^a	\$██████	\$██████	\$██████	████	████	████	\$██████
RFS and OS start to converge at Year █, converge at Year █ ^a	\$██████	\$██████	\$██████	████	████	████	\$██████
Extrapolation time point for RFS (base case: █ months)							
█ months	\$██████	\$██████	\$██████	████	████	████	\$██████
Extrapolation time point for OS (█ months)							
█ months	\$██████	\$██████	\$██████	████	████	████	\$██████
Cost for DAB+TRAM (base case: DAB+TRAM daily dose as observed in Trial COMBI-AD (no drug wastage), RFS in Year 1 as proxy for time on treatment with DAB+TRAM)							
PI recommended dose for DAB+TRAM ^b	\$██████	\$██████	\$██████	████	████	████	\$██████
PI recommended dose regimen + median treatment duration ^c	\$██████	\$██████	\$██████	████	████	████	\$██████
PI recommended dose regimen + mean treatment duration ^d	\$██████	\$██████	\$██████	████	████	████	\$██████
Costs for pembrolizumab, nivolumab, ipilimumab and fotemustine as post-recurrence treatment (base case: PBS-listed prices)							
Prices reduced by 50%	\$██████	\$██████	\$██████	████	████	████	\$██████
Age of modelled population (base case: 50.4 years)							
63 years (AIHW 2017)	\$██████	\$██████	\$██████	████	████	████	\$██████

DAB+TRAM = dabrafenib+trametinib; OBS = observation; OS = overall survival; RFS = relapse-free survival

^a In the observation, the dependent gamma distribution was used from the extrapolation point to the end of the time horizon. As for DAB+TRAM, the parametric extrapolation was used until the start converging point, then a linear decrease of OS estimates was assumed until the convergence time point.

^b PI recommended dose for dabrafenib was 150 mg daily and 2 mg daily for trametinib

^c The median treatment duration in COMBI-AD is 11 months for both DAB and TRAM

^d The mean treatment duration in COMBI-AD is 8.2 months for DAB and 8.3 months for TRAM

Source: Table 3.9-1, pp180-181 of the submission and from additional sensitivity analyses performed during the evaluation.

The redacted table shows ICERs in the range of \$15,000/QALY to \$200,000/QALY.

6.63 Setting the RFS and OS curves of the two treatment arms to begin converging at Year █ with complete convergence at Year █ resulted in an ICER of \$45,000/QALY - \$75,000/QALY. Assuming an earlier convergence point at Year █, the ICER exceeded \$100,000/QALY.

6.64 If the PI recommended dose regimen for adjuvant dabrafenib+trametinib and the mean duration of treatment from COMBI-AD were used in the economic evaluation, the ICER reduced to \$15,000/QALY - \$45,000/QALY.

Drug cost/patient/course: \$██████

6.65 The drug cost per patient per course was based on:

- daily doses of █ mg for dabrafenib and █ mg for trametinib, as observed in COMBI-AD;

- the costs per milligram of dabrafenib (\$████) and trametinib (\$████) calculated using the proposed effective dispensed prices for maximum quantity (i.e. assuming no drug wastage); and
 - a treatment duration of 12 months for the adjuvant combination therapy.
- 6.66 The drug cost would be \$████, using the PI dosing and mean duration of treatment as observed in COMBI-AD (8.2 months for dabrafenib and 8.3 month for trametinib).
- 6.67 The drug cost in the model base case was less than \$10 million, based on the drug cost (assuming no drug wastage) and the modelled RFS (████ months) as proxy for treatment duration.

Estimated PBS usage & financial implications

- 6.68 This submission was not considered by DUSC.
- 6.69 The submission used an epidemiological approach to estimate the likely extent of use of adjuvant dabrafenib+trametinib and associated financial implications to the PBS/RPBS. The number of eligible patients was based on:
- An incident population newly diagnosed with melanoma, estimated from a linear extrapolation of the AIHW data on incident rate from 2000 to 2014 (Australian Cancer Incidence and Mortality book: melanoma of the skin) and the Australian Bureau of Statistics data on the projected Australian population.
 - Incident patients diagnosed with Stage III disease, based on the NSW Cancer registry which involved all cutaneous melanoma cases diagnosed between 2010 and 2014 (Cancer Institute NSW 2018).
 - Incident patients initially diagnosed with earlier stages of disease that progress to Stage III melanoma, using the truncated (10-year) RFS curves from the Sydney Melanoma Unit database for patients diagnosed with cutaneous melanoma in 1959-2002 with Stage I or II disease^{***}. The disease staging system (AJCC 6th edition) and melanoma treatments in this population were outdated. The submission estimated that, in patients with Stage III melanoma, approximately █████% presented with Stage III after progression from earlier stage disease. This figure was lower than the Melanoma Institute Australia (MIA) data on patients diagnosed between 1970 and 2013 (55%)^{†††}. The PSCR argued that the 55% refers to the percentage of patients who presented with Stage III recurrent disease, which would include patients previously diagnosed Stage III whose disease has recurred and therefore likely overestimates disease recurrence at an earlier stage. It argued that Kaplan-Meier survival curves from the 8th Edition International Melanoma Database (Gershenwald 2017) show relatively high melanoma-specific

^{***} Francken AB, Accortt NA, Shaw HM, Colman MH, Wiener M, Soong SJ, et al. Follow-up schedules after treatment for malignant melanoma. *Br J Surg*. 2008;95(11):1401-7.

^{†††} Haydu LE, Scolyer RA, Lo S, Quinn MJ, Saw RPM, Shannon KF, et al. Conditional survival: an assessment of the prognosis of patients at time points after initial diagnosis and treatment of locoregional melanoma metastasis. *Journal of Clinical Oncology*. 2017;35(15):1721-9.

survival (MSS) rates for Stage I and II melanoma patients. Patients with Stage I and Stage II disease had 5-year and 10-year MSS rates of 98% and 95%, 90% and 84%, respectively, which would suggest that progression to Stage III from earlier stages of disease would also be relatively low.

- The proportion of patients with resectable Stage III melanoma was sourced from a market research survey which involved 31 medical oncologists. The generalisability of the survey results was of concern given the low response rate (< 10%).
 - The proportion of patients with BRAF V600 positive melanoma was calculated using a prevalence rate (44.5%) previously accepted by the MSAC when it considered the funding of BRAF mutation testing in patients with locally advanced or metastatic melanoma for eligibility for dabrafenib treatment (Application 1172 PSD, April 2013 MSAC meeting).
- 6.70 The submission assumed an expected uptake rate of ■■■%, based on the expert opinion from the market research survey. It is unclear whether this uptake would be realised in practice. The rate of uptake is likely to be lower in some populations, e.g. older patients, those with autoimmune comorbidities, and those with lower-risk melanoma (Stage IIIA). The PSCR noted a high uptake rate is expected because no effective treatment option currently exists. The ESC noted the toxicity of dabrafenib+trametinib may impact on uptake, especially for patients with a relatively low risk of recurrence.
- 6.71 The mean treatment duration of adjuvant therapy with dabrafenib+trametinib was derived from Trial COMBI-AD (8.2 to 8.3 months). This was appropriate.
- 6.72 The number of cases of recurrent disease avoided was estimated on the basis of the difference in rates of distant metastasis-free survival (DMFS) at Year 3 between the dabrafenib+trametinib and placebo arms reported in the COMBI-AD trial (14%). The absolute difference in DMFS rates between the two treatment groups decreased over time. The selection of Year 3 data was not justified. More importantly, DMFS is not a reasonable proxy for the avoidance of subsequent treatments in the unresectable or metastatic setting, as patients with unresectable regional recurrent disease are also eligible for post-recurrence anti-cancer medicines.
- 6.73 The submission indicated that BRAF±MEK inhibitors were first-line treatment for unresectable BRAF positive melanoma. The cost offsets associated with the proposed listing of adjuvant dabrafenib+trametinib were estimated by applying the number of patients avoiding distant metastasis to the costs of dabrafenib±trametinib in the unresectable or metastatic setting. The submission only considered the incremental number of patients who experience melanoma recurrence and receive subsequent dabrafenib+trametinib between the scenarios with and without adjuvant dabrafenib+trametinib. This implicitly assumed that the pattern of use of post-recurrence medicines (e.g. targeted therapies, immunotherapies and chemotherapies) in other patients with recurrent disease is the same between the

two scenarios. This is unlikely to occur in clinical practice and is inconsistent with the COMBI-AD trial and economic model.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed ^a	█	█	█	█	█	█
Estimated financial implications of dabrafenib+trametinib in the adjuvant setting						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments	\$ █	\$ █	-\$ █	-\$ █	\$ █	\$ █
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated financial implications for dabrafenib+trametinib in the unresectable or metastatic setting						
Cost to PBS/RPBS Revised ^b	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments Revised ^b	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost to PBS/RPBS less copayments Revised ^b	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net financial implications						
Net cost to PBS/RPBS Revised ^b	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS/RPBS/MBS Revised ^b	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Assuming █ scripts per year for dabrafenib and █ scripts per year for trametinib

^b Correcting the treatment duration for dabrafenib+trametinib in the unresectable or metastatic setting: █ months instead of █ months

Source: Table compiled during the evaluation, Table 4-9, p193, Table 4-10, p194, Table 4-12, p194, p4-13, p194, Table 4-19, p198, Table 4-20, p198, and Table 4-30, p202 of the submission.

The redacted table shows that at Year 6, the estimated number of patients was less than \$10,000 and the net cost to the PBS would be \$10 to \$20 million.

6.74 The submission could have underestimated or overestimated the cost implications to the PBS/RPBS associated with the proposed listing of adjuvant dabrafenib+trametinib. The main areas of uncertainty in the financial analyses were:

- the number of melanoma patients who are diagnosed with earlier stage disease and subsequently progress to Stage III disease;
- the uptake of dabrafenib+trametinib in the adjuvant setting; and
- the extent of utilisation of post-recurrence anti-cancer medicines by treatment year in scenarios with and without the listing of adjuvant dabrafenib+trametinib.

6.75 MBS costs for BRAF testing in the adjuvant setting and monitoring of AEs were included in the financial analysis. The submission did not provide the estimated MBS implications relating to BRAF testing in the unresectable or metastatic setting, disease

monitoring, management of AEs and subsequent surgery/radiotherapy for treatment of melanoma recurrence.

Financial Management – Risk Sharing Arrangements

- 6.76 The submission did not provide any information on a potential Risk Sharing Arrangement (RSA) for dabrafenib+trametinib as adjuvant treatment for completely resected Stage III BRAF positive melanoma.
- 6.77 A RSA, in the form of financial caps, applies to targeted therapies for treatment of BRAF positive unresectable Stage III or Stage IV melanoma, which is shared by the sponsors for dabrafenib+trametinib and vemurafenib+cobimetinib. There is also a RSA for PD-1 inhibitors (i.e. nivolumab and pembrolizumab) and for ipilimumab. The availability of dabrafenib+trametinib at an earlier stage of melanoma will affect the extent of utilisation and, thus, the financial implications for all of the above medicines for unresectable Stage III or Stage IV melanoma. The financial estimates presented in the submission considered reduced use of dabrafenib+trametinib for unresectable Stage III or IV disease but not reduced use of PD-1 inhibitors or ipilimumab.
- 6.78 The PBAC considered that the existing RSA should be extended to incorporate the expansion of the indication. To mitigate the uncertainty surrounding the extent of use of BRAF/MEK inhibitors in both the adjuvant and unresectable or metastatic settings, the PBAC considered that a new Deed should be negotiated that combines caps across the current PBS indication in unresectable disease with the proposed adjuvant indication. The PBAC considered that the new Deed should include hard caps with 100% rebates.

For more detail on PBAC's view, see Section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC deferred making a decision regarding the listing of dabrafenib plus trametinib as adjuvant treatment for BRAF V600 mutation positive patients with completely resected Stage III melanoma. In deciding to defer, the PBAC acknowledged that there was a high unmet clinical need for effective therapies to reduce the risk of recurrence for patients with resected Stage III melanoma. The PBAC considered it likely that adjuvant dabrafenib+trametinib provides, for some patients with Stage IIIB, IIIC or IIID disease, a significant improvement in efficacy over routine follow-up, in terms of recurrence-free survival (RFS), and a likely benefit in terms of overall survival (OS) although there are currently limited data. However, the results of the modelled economic evaluation were unreliable and resulted in an uncertain cost-effectiveness ratio.
- 7.2 The PBAC acknowledged the consumer comments, which were supportive of the PBS listing. In particular, the PBAC noted comments that there are no available PBS-subsidised adjuvant treatment options for melanoma, that dabrafenib+trametinib are oral agents, and that side effects range from mild to severe, but are manageable.

- 7.3 In terms of the clinical place, the PBAC noted the submission proposed that dabrafenib+trametinib would supplement routine care in Stage III resected BRAF positive patients who were naïve to dabrafenib+trametinib therapy, and that patients treated with dabrafenib+trametinib in the adjuvant setting would continue to be eligible to receive dabrafenib (with or without trametinib) in the unresectable or metastatic setting if they completed the 12 month adjuvant course without disease progression. The PBAC noted that limited clinical evidence was presented to support retreatment. However, the PBAC considered that it would be clinically inappropriate to prevent retreatment if a patient had responded well to adjuvant therapy.
- 7.4 The PBAC noted that the requested maximum quantities and repeats were sufficient for the recommended dosing schedule in the approved TGA Product Information. The PBAC noted that the continuing phase allowed for 5 repeats across all strengths (sufficient for 6 months therapy). However, the PBAC considered that patients may require more regular monitoring to determine any ongoing need for dose reduction. Therefore, the PBAC advised that 3 repeats would be more appropriate in the continuing phase (as per the initial phase). In addition, the PBAC considered that an Authority Required (telephone) would be appropriate for the initial supply to help reduce leakage into patients with Stage IIIA disease and the continuing supply to ensure treatment was capped at 12 months.
- 7.5 The PBAC foreshadowed that PBS-subsidised treatment in the adjuvant setting should be restricted to patients with Stage IIIB, IIIC and IIID (staged using the 8th edition of the AJCC melanoma staging system). This was mainly on the basis of patients with Stage IIIA disease with metastases ≤ 1 mm being excluded from the COMBI-AD trial, and patients with Stage IIIA disease with metastases > 1 mm having a relatively low risk of recurrence and the incremental effectiveness of dabrafenib+trametinib in these patients being uncertain (see below for further discussion).
- 7.6 The PBAC considered patients classified as having Stage IIIA disease at the time of excision of the primary tumour, and hence not eligible for adjuvant treatment, should be eligible for adjuvant treatment if and when they meet the criteria for Stage IIIB, IIIC or IIID disease and undergo a salvage nodal resection.
- 7.7 Noting that complete lymph node dissection (CLND) at the time of excision of the primary tumour was no longer standard of care for all patients with a positive sentinel lymph node, the PBAC considered that "completely resected disease" would, in practice, include all patients with a wide excision of the primary tumour and either CLND or sentinel lymph node biopsy (or both). The PBAC noted that, when the COMBI-AD trial was designed, CLND was considered standard practice and 98% of the trial participants had undergone CLND. Allowing treatment in patients without CLND thus impacts on the applicability of the COMBI-AD trial results to the PBS population as the effectiveness of dabrafenib+trametinib in these patients is unknown. However, it is currently unknown what proportion of patients will forgo a CLND in clinical practice as, although in the MSLT-II trial an improvement in melanoma-specific survival was not demonstrated with immediate CLND, immediate CLND did increase the rate of regional disease control and provided prognostic information in terms of disease in

non-sentinel nodes. The PBAC further noted the value of CLND is currently being debated in the clinical literature, and that immediate CLND is standard of care for patients presenting with clinically positive lymph nodes, and therefore more likely to be undertaken in patients with Stage IIIB, IIIC or IIID disease.

- 7.8 The PBAC considered that the nominated comparator, observation, was reasonable in this submission.
- 7.9 The submission was based on one head-to-head trial, COMBI-AD (N = 870), comparing dabrafenib+trametinib to placebo for the adjuvant treatment of Stage III patients with BRAF V600 E/K mutation positive cutaneous melanoma after complete surgical resection.
- 7.10 COMBI-AD classified melanoma stage using the 7th edition of the AJCC melanoma staging system, which has three prognostic Stage III subgroups (IIIA, IIIB and IIIC). The PBAC noted that the submission presented a comparison of disease stage at baseline in COMBI-AD using the 7th and 8th editions and the Australian population using the 8th edition of the AJCC staging system (see Table 4). The PBAC noted that, when classified using the 8th edition, the proportion of trial patients with Stage IIIA (metastases > 1 mm) disease was approximately 10%, and that patients with Stage IIID disease were potentially underrepresented in the COMBI-AD trial (approximately 5% compared with 23% in Australian clinical practice).
- 7.11 The primary outcome of COMBI-AD was relapse-free survival (RFS). At the median duration of follow-up (34 months for treatment arm and 33 months for placebo arm), the median RFS for the placebo arm was 16.6 months (95% CI: 12.7, 22.1) and median RFS for the dabrafenib+trametinib arm had not been reached (HR = 0.47; 95% CI: 0.39, 0.58). The PBAC noted that an updated analysis (at 44 months follow-up for the treatment arm and 42 months for placebo) showed similar results. The PBAC considered that the submission's claim that dabrafenib+trametinib was superior to placebo in terms of RFS, based on the analysis of COMBI-AD, was reasonable for the trial population. However, due to the immaturity of the trial data, the PBAC considered that the magnitude of the treatment effect was uncertain.
- 7.12 The PBAC noted that Hauschild (2018) reported a *post hoc* subgroup analysis of the updated RFS data conducted on the basis of baseline disease staging according to the 8th edition of the AJCC staging system. The PBAC noted that the RFS rate in the placebo arm at 3 years varied from 71% for Stage IIIA to 18% for Stage IIID. Furthermore, the PBAC noted that the absolute difference in RFS rates between treatment and placebo at 3 years varied from 13% for Stage IIIA to 25% for Stage IIID. The PBAC considered that the absolute RFS benefit and any potential OS benefit in the Stage IIIA subgroup to be particularly uncertain and likely to be modest, and not cost-effective at the same price as for Stages IIIB, IIIC and IIID. The benefit of adjuvant treatment in patients with Stage IIIA with metastases \leq 1 mm was unknown as they were not represented in COMBI-AD. The PBAC considered that use of adjuvant dabrafenib+trametinib would be most beneficial and cost-effective in patients with Stage IIIB, IIIC and IIID disease.

- 7.13 The PBAC noted that although interim OS results were available, the median OS had not been reached in either arm. Although the HR was statistically significant (HR = 0.57; 95% CI: 0.42, 0.79; p = 0.0006), it did not meet the pre-specified threshold for the first interim analysis (p = 0.00019). The PBAC considered that there was insufficient data to determine the magnitude of any OS benefit or whether dabrafenib+trametinib is curative in some patients, as opposed to delaying recurrence. The PBAC noted that a second interim OS analysis would be available in [REDACTED], and advised that, if listed, the sponsor should provide these results to the PBAC.
- 7.14 The PBAC considered that the claim of inferior comparative safety was reasonable, noting that no new safety signals were identified in the adjuvant setting.
- 7.15 The PBAC agreed with the ESC in considering that the economic model structure and inputs may not accurately reflect the outcomes of patients treated in the adjuvant setting over the [REDACTED] year time horizon, noting that the resulting ICER was highly sensitive to changes in convergence of the modelled RFS and OS curves. The PBAC advised that the following re-specifications to the model structure and inputs would result in a more reliable ICER:
- The modelled RFS and OS curves should converge from [REDACTED] to [REDACTED] years to reflect the uncertainty and immaturity of the data, in particular the modelled OS data were considered unreliable as it was based on events in 14% of patients in the dabrafenib+trametinib arm and 22% of patients in the placebo arm;
 - Treatment duration should be based on the mean duration of treatment observed in COMBI-AD (8.2 months for dabrafenib and 8.3 months for trametinib), rather than the modelled RFS ([REDACTED] months); and
 - In order to account for wastage, treatment doses should be based on the TGA approved Product Information doses, rather than the average doses in the trial.
- 7.16 The PBAC noted that with convergence of the RFS and OS curves the ICER was sensitive to the utility values, and that the small utility gains assumed for avoiding recurrence were likely underestimated in the model. The PBAC considered that it may be reasonable for the respecified scenario (as outlined in paragraph 7.15) to use utility values that better reflect the quality of life benefits of avoiding recurrence.
- 7.17 The PBAC, noting the uncertainty with the available clinical data and that it had previously accepted more conservative ICERs for adjuvant treatments for early breast cancer, considered that a reasonable ICER for adjuvant melanoma therapy would be less than \$15,000 to \$45,000 per QALY. The PBAC also noted that use of the published prices for pembrolizumab, nivolumab and ipilimumab as subsequent treatments for unresectable or metastatic disease increased the ICER, and advised that this would be taken into account when considering any revised proposal from the sponsor.
- 7.18 The PBAC considered that the estimated number of patients likely to be treated with dabrafenib+trametinib were uncertain, and the following issues should be revised in a resubmission:

- The use of outdated data (from 1959 to 2002, and based on the 6th edition of the AJCC staging system) to calculate the number of patients diagnosed with earlier stages of disease that would progress to Stage III disease;
 - a high assumed uptake rate of dabrafenib+trametinib in the adjuvant setting (■%);
 - the inclusion of patients with Stage IIIA disease; and
 - the non-inclusion of grandfathered patients.
- 7.19 The PBAC advised that the financial estimates should be updated to align with the foreshadowed changes to the restrictions, which would exclude Stage IIIA patients, but allow retreatment with dabrafenib±trametinib in the unresectable setting.
- 7.20 The PBAC considered that in the context of the uncertain use across the adjuvant and unresectable or metastatic settings, a Risk Sharing Arrangement (RSA) would be appropriate. The PBAC considered that any RSA should also include the current unresectable setting and include hard caps with 100% rebates.
- 7.21 The PBAC advised that a minor submission could be used to provide updated restrictions, address the uncertainty in the ICER, provide updated financial estimates and provide an RSA proposal.

Outcome:

Deferred

8 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.

9 Sponsor's Comment

Novartis are committed to working with the PBAC to achieve agreement on sustainable PBS listing conditions for dabrafenib and trametinib at the earliest opportunity.