

## **4.03 NIVOLUMAB,**

**Injection concentrate for I.V. infusion 40 mg in 4 mL,**

**100 mg in 10 mL,**

**Opdivo<sup>®</sup>,**

**Bristol-Myers Squibb Australia Pty Ltd**

### **1 Purpose of Application**

- 1.1 Nivolumab as an adjuvant treatment for completely resected Stage IIIB, IIIC, IIID or Stage IV melanoma was deferred at the July 2019 PBAC meeting to allow for further discussions regarding an acceptable price and Risk Sharing Arrangement (RSA).
- 1.2 Consistent with the PBAC's advice, the reconsideration of the July 2019 deferral (hereafter referred to as the deferral proposal) included:
  - Listing nivolumab on a cost-minimisation basis to dabrafenib+trametinib (DAB+TRAM) for the BRAF mutant population (paragraph 5.12, Nivolumab Public Summary Document (PSD), July 2019);
  - Listing nivolumab on a cost-effectiveness basis for the BRAF wild type population (paragraph 5.11, Nivolumab PSD, July 2019); and
  - A RSA consisting of subsidisation caps across the adjuvant and unresectable or metastatic settings, beyond which █████% rebates would apply (paragraph 5.15, Nivolumab PSD, July 2019).

### **2 Background**

- 2.1 Nivolumab for the adjuvant treatment of melanoma has been considered by the PBAC twice previously, as a major submission in July 2018 and as a minor resubmission in July 2019.
- 2.2 A major submission to extend the restrictions of nivolumab monotherapy and nivolumab plus ipilimumab combination therapy to allow their use as first-line treatment options in BRAF mutant patients in the unresectable or metastatic setting was also considered at the November 2019 PBAC meeting (item 7.07).
- 2.3 A minor submission for pembrolizumab for the treatment of adjuvant melanoma was also considered at the November 2019 PBAC meeting (item 7.12).

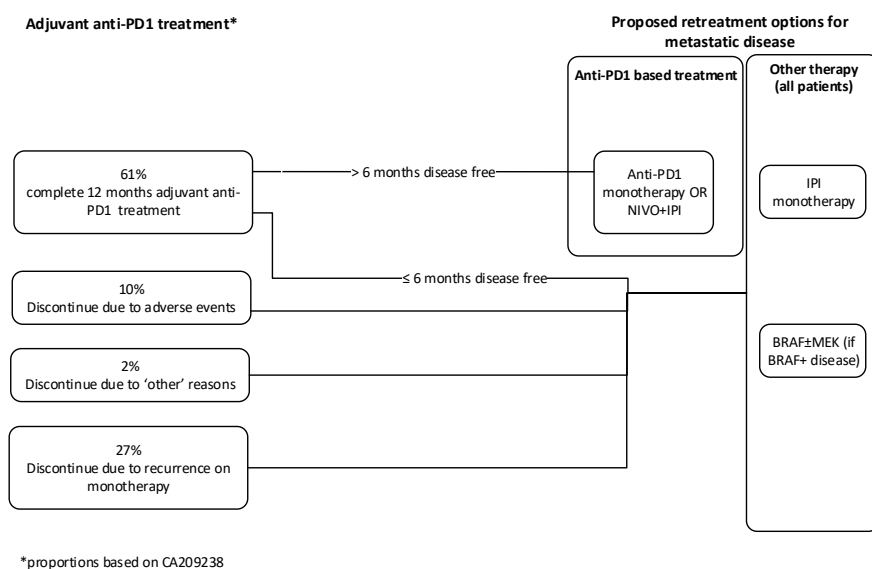
*For more detail on PBAC's view, see section 5 PBAC outcome.*

### 3 Requested listing

3.1 The sponsor raised concerns regarding the flow-on restriction changes to the current PBS listing of nivolumab (and pembrolizumab) in the unresectable or metastatic setting recommended at the July 2019 PBAC meeting.

3.2 Figure 1 illustrates the sponsor’s understanding of the treatment algorithm based on the July 2019 PBAC PSD.

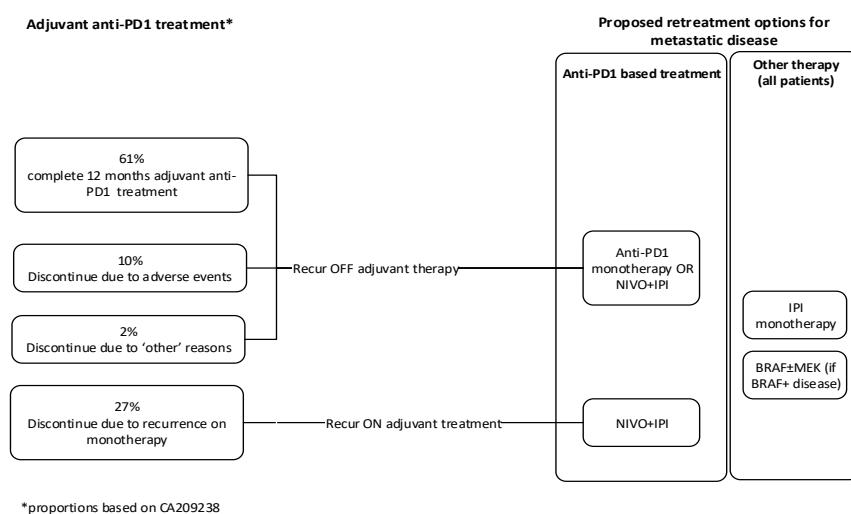
**Figure 1: Sponsor’s interpretation of retreatment options in the unresectable or metastatic setting following adjuvant anti-PD1 therapy**



IPI = ipilimumab; NIVO = nivolumab  
 Source: Figure 1, Attachment 5 of the nivolumab proposal

3.3 Figure 2 illustrates the sponsor’s position on the appropriate retreatment options for patients who have received adjuvant programmed cell death-1 (PD-1) inhibitor therapy and experience disease recurrence leading to a need for subsequent metastatic treatment.

Figure 2: Sponsor's position on the retreatment options in the unresectable or metastatic setting following adjuvant anti-PD1 therapy



IPI = ipilimumab; NIVO = nivolumab

Source: Figure 2, Attachment 5 of the nivolumab proposal

3.4 With respect to the flow-on restriction changes recommended at the July 2019 meeting the sponsor sought clarification regarding:

- The rationale for the clinical criteria stipulating retreatment with the same class of drug only if a patient had not experienced disease recurrence within six months post completion of adjuvant treatment. This PBAC recognised the uncertainty associated with the inclusion of a recurrence free interval in the restriction, but noted that this was consistent with the DAB+TRAM restriction changes in the unresectable or metastatic setting and with the design of the KN054 trial assessing pembrolizumab for the adjuvant treatment of melanoma. The PBAC advised that it would be willing to review the six month recurrence free interval for retreatment with the same class of drug if data was provided that supported the efficacy and cost-effectiveness of retreatment of patients who relapsed on or soon after completion of adjuvant treatment;
- Whether the changes proposed for the clinical criteria for nivolumab monotherapy apply to the use of nivolumab plus ipilimumab. The PBAC noted that the proposed restriction precluded patients who received nivolumab in the adjuvant setting and had a recurrence within six months of completing treatment, from receiving nivolumab+ipilimumab in the unresectable setting. Noting the paucity of data presented in the pre-PBAC response to support the repeated use of PD-1 inhibitor therapy (either as monotherapy or in combination) in patients who progressed while on, or shortly after completing, adjuvant PD-1 inhibitor monotherapy, the PBAC considered that the proposed restriction was reasonable. In addition, the

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PBAC noted that no data was provided to suggest that nivolumab+ipilimumab was superior to ipilimumab monotherapy following adjuvant PD-1 inhibitor treatment;

- The definition of ‘completion of treatment’ and whether a patient who misses doses (e.g. to wait for resolution of toxicity) during the treatment period, but essentially completes a 12 months period of therapy, is considered ‘completed’. The PBAC noted that the flow-on dabrafenib restriction for use in the unresectable or metastatic setting does not include a definition for ‘completion of treatment’. The PBAC considered that treatment should consist of 12 months of active therapy and recommended changing the restriction to state ‘Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy’; and
- Whether there could be potential exemptions to the proposed clinical criteria, including for patients who discontinued adjuvant treatment for reasons other than disease progression (e.g. intolerance, patient choice). The PBAC noted that the flow-on dabrafenib restrictions for use in the unresectable or metastatic setting do not include exemptions. Noting the paucity of available evidence to support the same level of benefit soon after exposure to the same class of drug, the PBAC considered that the lack of exemptions was appropriate.

3.5 The PBAC considered that flow-on changes for nivolumab, ipilimumab, pembrolizumab and the BRAF inhibitor listings in the unresectable or metastatic setting would be required. The PBAC recommended that these be implemented in conjunction with the recommendation to extend the listings of nivolumab and nivolumab+ipilimumab to allow first-line treatment in the unresectable or metastatic setting in BRAF mutant patients.

3.6 The proposed restrictions for nivolumab for adjuvant treatment are presented below.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
NIVOLUMAB 40 mg/4 mL injection, 4 mL vial 100 mg/10 mL injection, 10 mg vial	480 mg	11	Published \$10,053.46 (public) \$10,232.76 (private)	Opdivo® Bristol-Myers Squibb
			Effective \$ TBD (public) \$ TBD (private)	

<b>Category/Program:</b>	Section 100 Efficient Funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Resected Stage IIIB, IIIC, IIID or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Resected Stage IIIB, IIIC, IIID or Stage IV malignant melanoma
<b>Restriction level:</b>	<input checked="" type="checkbox"/> Authority Required (Telephone)

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<b>Clinical criteria:</b>	<p>The treatment must be adjuvant to complete surgical resection; AND Patient must have a WHO performance status of 1 or less at the commencement of treatment with this drug, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must not have received prior PBS-subsidised treatment for this condition, AND Treatment must commence within 12 weeks of complete resection, unless delay is necessary due to post-surgery recovery, AND The treatment must cease if disease recurs, AND The treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC, IIID or Stage IV melanoma, AND The treatment must not exceed a dose of 3 mg/kg or 240 mg every two weeks or 480 mg every four weeks</p>
<b>Notes:</b>	<p>No increase in the maximum quantity or number of units may be authorised. No increase in the number of repeats may be authorised. Special Pricing Arrangements apply.</p>

<b>Category/Program</b>	Section 100 Efficient Funding of Chemotherapy
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Resected Stage IIIB, IIIC, IIID or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Resected Stage IIIB, IIIC, IIID or Stage IV malignant melanoma
<b>Treatment phase:</b>	Grandfathered treatment
<b>Restriction level:</b>	<input checked="" type="checkbox"/> Authority Required (Telephone)
<b>Clinical criteria:</b>	<p>Patient must have previously received non-PBS subsidised drug for adjuvant treatment following complete surgical resection prior to [date of PBS listing], AND The patient must have a WHO performance status of 0 or 1 at the time non-PBS subsidised treatment with this drug for this condition was initiated, AND Patient must not have experienced disease recurrence, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have commenced non-PBS subsidised treatment within 12 weeks of complete surgical resection, unless delay was necessary due to post-surgery recovery, AND The treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC, IIID or Stage IV melanoma, AND The treatment must not exceed a dose of 3 mg/kg or 240 mg every two weeks or 480 mg every four weeks.</p>
<b>Notes:</b>	<p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

*For more detail on PBAC's view, see section 5 PBAC outcome.*

## 4 Consideration of the evidence

### Sponsor hearing

4.1 There was no hearing for this item as it was a reconsideration of a deferral.

### Consumer comments

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

### Weighted effective price

4.3 Two cost-minimisation analyses comparing nivolumab with DAB+TRAM were presented in the deferral proposal. These analyses were included in the July 2019 nivolumab minor overview and have been previously considered by the PBAC. Both analyses used the TGA approved Product Information doses of dabrafenib (150 mg twice daily), trametinib (2 mg once daily) and nivolumab (150 mg every four weeks) in order to account for wastage.

4.4 The first analysis did not consider treatment duration, and was based on the maximum treatment duration of 12 months for both nivolumab and DAB+TRAM (Table 1). The equi-effective doses for this analysis are:

Nivolumab 3 mg/kg Q2W OR 240 mg Q2W OR 480 mg Q4W =

Dabrafenib 150 mg BD + trametinib 2 mg OD

**Table 1: Cost-minimised price of nivolumab (480 mg Q4W) to dabrafenib+trametinib, without consideration of treatment duration, using the published AEMPs (1 November 2019)**

A	AEMP for 30 day supply of DAB	-	\$8,181.56
B	AEMP for 30 day supply of TRAM	-	\$8,612.17
C	AEMP for 30 day supply of DAB+TRAM	A + B	\$16,793.73
D	AEMP for years supply of DAB+TRAM	C * 12.175 <sup>a</sup>	\$204,463.66
E	Dose of NIVO	-	480 mg every four weeks
F	Yearly dose of NIVO	E * 13.04 <sup>b</sup>	6,261.43 mg
G	Cost of NIVO administration per year	\$66.10 <sup>c</sup> * 13.04 <sup>b</sup>	\$862.25
H	Cost of NIVO year	D – G	\$203,601.41
I	Cost of NIVO per mg	H / F	\$32.52/mg
J	<b>Cost minimised AEMP per 40 mg vial of NIVO</b>	<b>I * 40</b>	<b>\$1,300.67</b>
K	<b>Cost minimised AEMP per 100 mg vial of NIVO</b>	<b>I * 100</b>	<b>\$3,251.68</b>

AEMP = approved ex-manufacturer price; DAB = dabrafenib; NIVO = nivolumab; TRAM = trametinib

a 12.175 = 365.25 days per year / 30 day supply

b 13.04 = 365.25 days per year / 28 day dosing

c MBS item 13915 (100% benefit)

4.5 The sponsor noted that the effective approved ex-manufacturer price (AEMP) of nivolumab in patients with BRAF mutant disease would likely need to be adjusted based on the results of the cost-minimisation analysis using the effective AEMPs of DAB+TRAM.

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- 4.6 The second analysis considered treatment duration, and is based on the mean treatment durations observed in the key clinical trials.
- 4.7 Given adjuvant therapy is a fixed 12 month course of treatment, the PBAC considered that it was reasonable to conduct the cost-minimisation analysis between nivolumab and DAB+TRAM for BRAF mutant patients without consideration of the mean trial treatment durations.
- 4.8 Table 2 provides a summary of the proposed weighted nivolumab melanoma price across the adjuvant and unresectable or metastatic settings. Acknowledging that DAB+TRAM have Special Pricing Arrangements and that the price of nivolumab in BRAF mutant patients was likely to change, the calculations used the proposed effective AEMP of nivolumab in BRAF wild type patients as a place-holder price for BRAF mutant patients. The effective AEMP of nivolumab in patients with BRAF wild type disease (\$ [REDACTED]) was consistent with the price proposed in the July 2019 minor resubmission and was considered acceptable by the PBAC. The effective AEMP of nivolumab in the unresectable or metastatic setting was the 1 September 2019 effective AEMP.
- 4.9 The proposed weightings of [REDACTED]%, [REDACTED]% and [REDACTED]% for the adjuvant BRAF mutant, adjuvant BRAF wild type and unresectable settings, respectively, were based on the estimated effective expenditure for each of the settings over the first five years following listing for adjuvant treatment. The Secretariat noted that this may not have been appropriate as using effective indication-specific expenditure resulted in a higher weighting for indications with higher effective prices. The Department's usual approach is for weighted prices to be calculated based on prescription volume or published expenditure for each indication.
- 4.10 Prescription volumes for projected use in the unresectable setting were not calculated, rather the expenditure in the metastatic setting was based on extrapolation of the current expenditure caps. The sponsor stated conversion to prescription volumes would include: i) adjustments to account for the different dose frequencies of nivolumab and pembrolizumab; ii) application of growth in unit volume in a far from stable market; and iii) consideration of caps being exceeded in the first four years of listing. The sponsor considered this would introduce a significant amount of additional complexity and uncertainty and therefore proposed the weightings to be based on relative expenditure. The Secretariat noted that it would be possible for the effect of the different effective prices in each setting to be removed from the weighting (based on relative expenditure), and this would better represent the estimated proportion of drug utilisation for each indication. The recalculated weights and weighted price are presented in Table 2.
- 4.11 The weighted price does not impact on the estimated expenditure for nivolumab in the adjuvant setting as this was calculated based on the estimated number of adjuvant prescriptions multiplied by the adjuvant melanoma price. Use of the weighted price

would impact on the rate at which the subsidisation caps (i.e. the RSA across both the adjuvant and unresectable settings) would be reached (with a higher weighted price the caps would be reached more quickly), and if the caps were not reached this would impact on the total expenditure (the expenditure would be the higher weighted price multiplied by the number of prescriptions).

- 4.12 The PBAC noted that weighting based on prescription volumes was the usual method for calculating weighted prices and minimised the risk to government in the case of the subsidisation caps not being reached.

**Table 2: Weighted effective AEMPs for nivolumab across the adjuvant and unresectable or metastatic settings calculated based on effective expenditure and prescription volume for each setting**

	Adjuvant melanoma		Unresectable or metastatic melanoma
	BRAF MT	BRAF WT	
Effective AEMP per 100 mg vial	\$ [REDACTED]*	\$ [REDACTED]	\$ [REDACTED]
<b>Based on effective expenditure across settings (as per deferral proposal)</b>			
Weighting based on expenditure caps	[REDACTED]%	[REDACTED]%	[REDACTED]%
Weighted AEMP per 100 mg vial	\$ [REDACTED]*		
<b>Based on prescription volume for each setting (as per Secretariat)</b>			
Weighting excluding effective AEMP	[REDACTED]#	[REDACTED]##	[REDACTED]###
Weighted AEMP per 100 mg vial	\$ [REDACTED]*		

\* Price to be adjusted based on the results of the cost-minimisation analysis with dabrafenib+trametinib.

# calculated as  $(\text{[REDACTED]}) / (\text{[REDACTED]} + \text{[REDACTED]} + \text{[REDACTED]}) = \text{[REDACTED]}$

## calculated as  $(\text{[REDACTED]}) / (\text{[REDACTED]} + \text{[REDACTED]} + \text{[REDACTED]}) = \text{[REDACTED]}$

### calculated as  $(\text{[REDACTED]}) / (\text{[REDACTED]} + \text{[REDACTED]} + \text{[REDACTED]}) = \text{[REDACTED]}$

AEMP = approved ex-manufacturer price; MT = mutant melanoma (i.e. BRAF positive); WT = wild type melanoma (i.e. BRAF negative)

Source: Table 1, p1 of the August 2019 nivolumab proposal

### **Estimated PBS usage & financial implications**

- 4.13 Noting that a major submission to extend the PBS restrictions of nivolumab monotherapy and nivolumab+ipilimumab to allow first-line treatment in BRAF mutant patients in the unresectable or metastatic setting was also considered at the November 2019 meeting, and that both submissions proposed a RSA which incorporated both the adjuvant and unresectable or metastatic settings, the PBAC considered that the adjuvant and unresectable or metastatic populations should be calculated in a consistent manner across the submissions.

- 4.14 The sponsor provided amended financial estimates. A summary of the key assumptions and revisions is presented in Table 3.

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Table 3: Changes to key parameters employed in the financial estimates

	July 2019 minor resubmission	November 2019 deferral proposal	Rationale
Patients with resectable disease	Stage III: 86% Stage IV: 13%	Stage III: 81% Stage IV: 13%	Reducing the percent of Stage III patients with resectable disease is consistent with the PBAC recommendations
Patients eligible for adjuvant treatment	2020 [REDACTED] 2021 [REDACTED] 2022 [REDACTED] 2023 [REDACTED] 2024 [REDACTED] 2025 [REDACTED]	2020 [REDACTED] 2021 [REDACTED] 2022 [REDACTED] 2023 [REDACTED] 2024 [REDACTED] 2025 [REDACTED]	Reduction is due to reducing the percent of patients with resectable disease as above.
Uptake rate	90%	90%	Assumption
BRAF MT patients	-	44.5%	MSAC application 1172, April 2013
PD-1 uptake in BRAF MT patients	-	74.1%	Clinician survey
Patients receiving adjuvant treatment (number of grandfathered patients included)	2020 [REDACTED] 2021 [REDACTED] 2022 [REDACTED] 2023 [REDACTED] 2024 [REDACTED] 2025 [REDACTED]	2020 [REDACTED] 2021 [REDACTED] 2022 [REDACTED] 2023 [REDACTED] 2024 [REDACTED] 2025 [REDACTED]	Revised to exclude patients treated with DAB+TRAM
Nivolumab dosing	3 mg/kg Q2W: 100% 240 mg Q2W: - 480 mg Q4W: -	3 mg/kg Q2W: 5% 240 mg Q2W: 47% 480 mg Q4W: 48%	Revision as per PBAC recommendations. Based on sponsor PAP.

MSAC = Medicare Benefits Advisory Committee; MT = mutant melanoma (i.e. BRAF positive); PAP = patient access program; PBAC = Pharmaceutical Benefits Advisory Committee; PD-1 = programmed cell death 1 inhibitor; Q2W = every two weeks; Q4W = every four weeks  
Source: Table 2, p3 of the August 2019 nivolumab proposal

- 4.15 The sponsor provided an amended estimate of the proportion of Stage III patients with resectable disease. Although stating that the original estimate of 86%, which was based on a clinician survey, was reasonable and supported by SEER data that indicated that 89% of Stage III patients were resectable, a revised estimate of 81% was proposed. The PBAC considered that the revised estimate of 81% was a reasonable estimate of the proportion of Stage III patients with resectable disease.
- 4.16 Based on a previous MSAC consideration for BRAF mutation testing (Application 1172 PSC, April 2013 MSAC meeting) it was estimated that 44.5% of patients are BRAF mutant. The PBAC considered that it would be more reasonable to assume that 37.7% of patients were BRAF mutant, based on the results of an Australian cohort study<sup>1</sup>.
- 4.17 The uptake of PD-1 inhibitors in BRAF mutant patients was estimated to be 74.1%, based on the results of a survey of 143 medical oncologists, of which 32 (22%) clinicians responded. The low response rate was considered by the Economics Sub-Committee (ESC) to affect the representativeness of the sample and the generalisability to inform market shares. The PBAC previously considered that the

<sup>1</sup> Lyle M, Haydu LE, Menzies AM, et al. The molecular profile of metastatic melanoma in Australia. 2016; 48(2): 188-193

toxicity of DAB+TRAM would affect its uptake, especially in patients with a relatively low risk of recurrence (paragraph 6.70, Dabrafenib+trametinib PSD, March 2019). The PBAC considered that the uptake rate of PD-1 inhibitors in BRAF mutant patients of 74.1% was reasonable in the adjuvant setting.

- 4.18 The PBAC noted that the nivolumab dosing assumptions were based on patient data (27 June 2019) from the nivolumab Patient Access Program presented in the July 2019 pre-PBAC response. Although this was requested by the PBAC in July 2019 (paragraph 5.13, Nivolumab PSD, July 2019), on reconsideration, the PBAC determined that the four weekly dosing schedule would be the most highly utilised and that it would be more appropriate to use the estimates provided in the nivolumab flat dosing submission in March 2019 which assumed that 3.0% of patients would receive 3 mg/kg every two weeks, 9.0% would receive 240 mg every two weeks and 88.0% would receive 480 mg every four weeks.
- 4.19 The adjusted number of grandfathered patients (less than 500) was based on the number of infusions yet to be received by each monthly cohort of patients and the average number of infusions per patient per treatment course. A total of 500 – 5,000 patients have received adjuvant treatment with nivolumab in the 12 months since the Patient Access Program opened and it was anticipated that all those who were still receiving treatment at the time of PBS listing would be grandfathered onto the PBS.
- 4.20 The estimated financial impact of listing nivolumab on the PBS/RPBS presented in the deferral proposal is provided in Table 4.

**Table 4: Estimated use and financial impact of nivolumab**

	2020	2021	2022	2023	2024	2025
<b>July 2019 minor resubmission</b>						
Patients treated	██████████	██████████	██████████	██████████	██████████	██████████
Net effective cost to PBS/RPBS <sup>a</sup>	██████████	██████████	██████████	██████████	██████████	██████████
<b>November 2019 deferral proposal</b>						
Patients treated	██████████	██████████	██████████	██████████	██████████	██████████
Net effective cost to PBS/RPBS <sup>b</sup>	██████████	██████████	██████████	██████████	██████████	██████████

PBS = Pharmaceutical Benefits Advisory Committee; RPBS = Repatriation Pharmaceutical Benefits Advisory Committee

<sup>a</sup> Based on a mean dose per infusion of 253.99 mg

<sup>b</sup> Based on 5% of patients receiving 3 mg/kg (mean dose of 253.99 mg) Q2W, 47% receiving 240 mg Q2W and 48% receiving 480 mg Q4W  
Source: Table 6, p5 of the August 2019 nivolumab proposal

The redacted table shows that at Year 6, the estimated number of patients was 500 – 5,000 and the net cost to the PBS would be \$60 - \$70 million (July 2019 minor submission) and \$40 - \$50 million (November 2019).

### **Risk Sharing Arrangement**

- 4.21 As recommended in July 2019, the sponsor presented a revised RSA that encompassed adjuvant and unresectable or metastatic use of the PD-1 inhibitors (i.e. nivolumab and pembrolizumab). Any use beyond the proposed annual subsidisation caps would result in the application of a ██████% rebate.

4.22 The unresectable or metastatic component of the subsidisation cap was based on extrapolation of Commonwealth Expenditure, as per the current Deed of Agreement for PD-1 inhibitor therapies and which expires in August 2020, as outlined in Table 5.

**Table 5: Current PD-1 inhibitor subsidisation caps for unresectable or metastatic melanoma**

	Sep 15 – Aug 16	Sep 16 – Aug 17	Sep 17 – Aug 18	Sep 18 – Aug 19	Sep 19 – Aug 20
PD-1 subsidisation caps	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Annual growth	-	-	% [REDACTED]	% [REDACTED]	% [REDACTED]

PD-1 = programmed death-1 inhibitor

Source: Table 7, p6 of the August 2019 nivolumab proposal

4.23 The mean annual expenditure growth rate in the current expenditure caps for Years 3 to 5 is [REDACTED]%. This has been applied over the 6-year forecast period (per calendar year), as per Table 6.

**Table 6: Estimated future PD-1 inhibitor subsidisation caps for unresectable or metastatic melanoma, by calendar year**

	2019	2020	2021	2022	2023	2024	2025
PD-1 subsidisation caps	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

PD-1 = programmed death-1 inhibitor

Source: Table 8, p6 of the August 2019 nivolumab proposal

4.24 The sponsor considered that the annual growth rate of [REDACTED]% was conservative compared with a predicted growth of 6.9%, based on DUSC’s reported number of incident patients commencing PBS treatment for the period 2014 to 2017<sup>2</sup>. The Secretariat noted that over the period from 2014 to 2017 a number of new treatments became available which may have impacted on the growth rate, as only ipilimumab and dabrafenib were available in 2014.

4.25 The sponsor also noted the assumed growth rate of [REDACTED]% was substantially lower than the actual growth in PD-1 inhibitor expenditure for unresectable melanoma prior to rebates being applied (15.1% growth in Sep 2017 to Aug 2018 and 17.8% growth in Sep 2018 to Aug 2019).

4.26 The PBAC noted that the incidence of melanoma in Australia was increasing at a rate lower than [REDACTED]% - see Table 7. The PBAC considered that a growth rate of [REDACTED]%, which was the assumed annual growth rate of the unresectable or metastatic BRAF/MEK inhibitor treated population in the July 2019 minor resubmission and which was based on PBS data from January to June 2018, applied to the 6-year forecast would be more appropriate.

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<sup>2</sup> DUSC. Medicines for the treatment of melanoma. May 2018. Available at: <http://www.pbs.gov.au/industry/listing/participants/public-release-docs/2018-05/melanoma-review-DUSC-PRD-2018-06-final.pdf>

**Table 7: Incidence of melanoma in Australia**

Year	Incident cases	Growth
2010	11,509	-
2011	11,663	1.34%
2012	12,270	5.20%
2013	12,892	5.07%
2014	13,215	2.51%
2015	13,694	3.62%
2016	13,816	0.89%
2017	14,241	3.08%
2018	14,778	3.77%
2019	15,229	3.05%
<b>Average growth</b>		<b>3.17%</b>

Source: National Cancer Control Indicators for melanoma, published 13 Sep 2019. Available from: <https://ncci.cancer australia.gov.au/diagnosis/cancer-incidence/cancer-incidence>

- 4.27 The PBAC considered that that availability of BRAF+MEK and PD-1 inhibitors in the adjuvant setting was likely to result in a relative increase in usage of BRAF+MEK inhibitors compared to PD-1 inhibitors as first-line treatment in BRAF mutant patients in the unresectable and metastatic setting. This would be driven by the smaller proportion of patients receiving BRAF+MEK inhibitor adjuvant therapy (i.e. 100% - 74.1% = 23.9%). Based on the results of the clinician survey, the sponsor estimated that 63% to 70% of the BRAF mutant unresectable or metastatic population would receive a PD-1 inhibitor (either as monotherapy or as nivolumab in combination with ipilimumab) as first-line treatment. However, based on the proposed 74.1% rate of adjuvant PD-1 inhibitor use in BRAF mutant patients, the PBAC considered that the sponsor’s estimate for PD-1 inhibitor use (either as monotherapy or as nivolumab+ipilimumab) in the unresectable or metastatic setting was overestimated. The PBAC considered that an estimate of 50% to 60% of BRAF mutant unresectable or metastatic patients receiving PD-1 inhibitor treatment first-line was more appropriate.
- 4.28 The PBAC previously considered that the introduction of adjuvant therapy would result in a reduction in the number of patient treated in the unresectable or metastatic setting as they would avoid unresectable or metastatic recurrence (i.e. they would be cured). The PBAC considered that any reduction in use in the unresectable or metastatic setting was unlikely to be observed in the first year of the adjuvant listing but would be expected from the second year of adjuvant listing (paragraph 4.40, Nivolumab PSD, July 2019).
- 4.29 As per the July 2019 minor resubmission, the sponsor reduced the unresectable or metastatic subsidisation cap by █% per annum (█% x █% - see below) from Year 2 to account for patients who do not have a recurrence.
- 4.30 The July 2019 minor resubmission used data from New South Wales Cancer Statistics to estimate that approximately 66% of patients who died from melanoma had an

initial diagnosis of local or regional disease. The PBAC considered that this was reasonable.

- 4.31 The modelled economic evaluation in July 2019 found that the difference in distant metastases free survival at 10 years was 11%. The PBAC noted that the distant metastasis free survival difference did not include patients who were also free of local unresectable recurrence. In addition, the PBAC considered given the timeframe of the financial estimates that it would be more appropriate to use the difference in recurrence free and/or distant metastasis free survival over 2 to 5 years. Using the July 2019 economic model and differences at 2 and 5 years, the PBAC considered that it would be more reasonable to assume that [redacted] % to [redacted] % of patients would avoid unresectable or metastatic recurrence (local and/or distant) – see Table 8. Therefore, the PBAC considered that it would be more reasonable to reduce the unresectable or metastatic subsidisation cap by [redacted] % to [redacted] % to account for the patients avoiding unresectable or metastatic recurrence due to receiving adjuvant treatment.

**Table 8: Comparison of distant metastases free and recurrence free survival rates at 2, 5 and 10 years**

	DMFS model	Difference in survival
2 years	[redacted] % NIVO vs [redacted] % SOC	16.1%
5 years	[redacted] % NIVO vs [redacted] % SOC	15.5%
10 years	[redacted] % NIVO vs [redacted] % SOC	10.6%
	RFS model	
2 years	[redacted] % NIVO vs [redacted] % SOC	22.4%
5 years	[redacted] % NIVO vs [redacted] % SOC	20.4%
10 years	[redacted] % NIVO vs [redacted] % SOC	13.2%

DMFS = distant metastases free survival; NIVO = nivolumab; RFS = recurrence free survival; SOC = standard of care

Source: Attachment 1\_Section 3 economic model\_Jul19, MarkovModel\_NIVvBSC tab

- 4.32 Based on Figure 1 above, the deferral proposal estimated that 61% of patients complete 12 months of adjuvant PD-1 inhibitor therapy and 27% discontinue due to recurrence whilst on treatment. The PBAC therefore considered that at least 30% to 40% of patients would relapse whilst on, or within six months of completing, adjuvant therapy. Noting that 66% of patients who died from melanoma had an initial diagnosis of local or regional disease (paragraph 4.30), 37.7% of patients would be BRAF mutant and 74.1% of BRAF mutant patients would receive a PD-1 inhibitor as adjuvant therapy, the PBAC estimated that [redacted] % ( $[redacted] \times [redacted] \times [redacted] \times [redacted]$ ) to [redacted] % ( $[redacted] \times [redacted] \times [redacted] \times [redacted]$ ) of the unresectable or metastatic population would be ineligible to receive PD-1 inhibitor therapy. For the remaining 62.3% of BRAF wild type patients, [redacted] % ( $[redacted] \times [redacted] \times [redacted]$ ) to [redacted] % ( $[redacted] \times [redacted] \times [redacted]$ ) would be ineligible to receive PD-1 inhibitor treatment in the unresectable setting. Thus, in total, [redacted] % to [redacted] % of the unresectable or metastatic population would be ineligible to receive PD-1 inhibitor therapy.
- 4.33 The proposed RSA subsidisation caps, as provided in the deferral proposal, incorporated both the adjuvant and unresectable or metastatic settings, as shown in

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Table 9. The adjuvant component of the subsidisation caps was based on the cost to the PBS/RPBS as proposed by the submission in Table 4 above.

**Table 9: Proposed RSA subsidisation caps for the PD-1 inhibitors across the adjuvant and unresectable or metastatic settings**

	2020	2021	2022	2023	2024	2025
<b>Unresectable or metastatic setting</b>						
PD-1 subsidisation expenditure						
Reduction in use	0.0%	%	%	%	%	%
Expected reduction	-					
Total expenditure						
<b>Adjuvant setting</b>						
Total expenditure						
<b>Proposed PD-1 subsidisation cap</b>						
PD-1 subsidisation cap						

PD-1 = programmed death-1 inhibitor

Source: Table 11, p7 of the August 2019 nivolumab proposal

- 4.34 The PBAC considered that the adjuvant setting figures should be revised as per paragraphs 4.16 and 4.18 and the unresectable or metastatic setting figures should be revised as per paragraph 4.26, 4.27, 4.31 and 4.32.
- 4.35 Approximate numbers of patients receiving PD-1 inhibitors, using the PBAC proposed revisions, are presented in Table 10.
- 4.36 Approximate financial estimates, using the PBAC proposed revisions, are presented in Table 11.

**Table 10: Patients receiving PD-1 inhibitors across the adjuvant and unresectable or metastatic settings, as per the PBAC recommendations**

	Method	2020	2021	2022	2023	2024	2025
<b>Adjuvant setting</b>							
A	Eligible patients	-					
B	BRAF MT patients	A x 37.7%					
C	BRAF MT patients receiving PD-1	B x 74.1%					
D	BRAF MT grandfather patients	-					
E	BRAF WT patients	A x (1 - 37.7%)					
F	BRAF WT grandfather patients	-					
G	Total receiving PD-1	C + D + E + F					
<b>Unresectable setting</b>							
H	2019 eligible patients	2,188	-	-	-	-	-
I	Eligible patients	$\#_{(t-1)} \times (1 + 4.56\%)$					
J	BRAF MT first-line patients	As per PBAC submission for first-line treatment for BRAF MT patients (November 2019 meeting, item 7.07)					

BRAF MT = BRAF mutant; BRAF WT = BRAF wild type; PBAC = Pharmaceutical Benefits Advisory Committee; PD-1 = programmed death-1 inhibitor

Source: As per PBAC consideration

**Committee-In-Confidence information**

Table 11: Subsidisation caps across the adjuvant and unresectable or metastatic settings, as per the PBAC recommendations

	Method	2020	2021	2022	2023	2024	2025
<b>Adjuvant setting</b>							
K	BRAF MT patients	$(C + D) \times \$$ [redacted] <sup>a</sup>	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
L	BRAF WT patients	$(E + F) \times \$$ [redacted] <sup>b</sup>	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
M	Total cost	K + L	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>Unresectable or metastatic setting</b>							
N	2019 cap	\$ [redacted]	-	-	-	-	-
O	Cap growth	$\$(t-1) \times (1 + \text{[redacted]}\%)$	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
P	BRAF MT first line patients	As per PBAC submission for first-line treatment for BRAF MT patients (November 2019 meeting, item 7.07)					
Q	Offset due to adjuvant cure	[redacted]% to [redacted]% from Year 2 onwards					
R	Offset due to adjuvant early relapse	[redacted]% to [redacted]% from Year 1 onwards					
<b>Combined adjuvant and unresectable or metastatic setting</b>							
S	Total cap	Adjuvant melanoma total cost plus unresectable or metastatic total cost					

AEMP = approved ex-manufacturer price; BRAF MT = BRAF mutant; BRAF WT = BRAF wild type; DAB+TRAM = dabrafenib+trametinib; DPMA = dispensed price for maximum amount; NIVO = nivolumab; PBAC = Pharmaceutical Benefits Advisory Committee

<sup>a</sup> DPMA less co-payment, based on AEMP of \$ [redacted] per 100 mg NIVO as per cost-minimisation versus DAB+TRAM

<sup>b</sup> DPMA less co-payment, based on AEMP of \$ [redacted] per 100 mg NIVO

Source: As per PBAC consideration

**End Committee-in-Confidence information**

For more detail on PBAC's view, see section 5 PBAC outcome.

**5 PBAC Outcome**

5.1 The PBAC recommended the listing of nivolumab for the adjuvant treatment of completely resected Stage IIIB, IIIC, IIID or Stage IV malignant melanoma, on the basis that it should be available under Section 100 – Efficient Funding of Chemotherapy. The PBAC noted changes made to the economic analysis and considered that the uncertainty surrounding uptake in the adjuvant setting and changes to use in the unresectable or metastatic setting would be managed by subsidisation caps through a Risk Sharing Arrangement (RSA).

5.2 The PBAC noted that no additional clinical data was provided, but remained satisfied that nivolumab was non-inferior compared to dabrafenib+trametinib (DAB+TRAM) for BRAF mutant patients and superior compared to routine follow-up for BRAF wild type patients in terms of recurrence free survival. The PBAC noted that there was currently limited overall survival data. In terms of safety, the PBAC recalled that it previously considered that nivolumab was inferior to routine follow-up, and may be better

tolerated than DAB+TRAM.

- 5.3 The PBAC recalled that it had previously accepted the cost effectiveness analysis of nivolumab in BRAF wild type patients and had advised that if DAB+TRAM was listed on the PBS for the adjuvant treatment of BRAF mutant melanoma, it would be appropriate for nivolumab to be cost minimised to DAB+TRAM for the proportion of patients that were BRAF mutant positive. The PBAC considered that for BRAF mutant positive patients the equi-effective doses were:

Nivolumab 3 mg/kg every two weeks OR 240 mg every two weeks OR 480 mg every four weeks =

Dabrafenib 150 mg twice daily + Trametinib 2 mg once daily

- 5.4 The PBAC considered that as adjuvant therapy with both treatments is a fixed 12 month course, it was reasonable for the equi-effective doses to not reflect the mean treatment duration from the trials.
- 5.5 The PBAC noted that the deferral proposal provided a weighted price for nivolumab across the adjuvant and unresectable or metastatic settings. The PBAC noted that the weighting was based on estimated effective expenditure across the settings and advised that it would be more appropriate to base the weightings on prescription volumes. In addition, the PBAC noted that the weighted pricing proposal would have to be updated to include extended use in the first-line unresectable or metastatic setting for BRAF mutant patients associated with the November 2019 application for NIVO monotherapy and NIVO+IPI.
- 5.6 The PBAC noted that the estimated financial implications of listing nivolumab on the PBS for use in adjuvant melanoma had been updated from the July 2019 minor resubmission and considered that the following assumptions were reasonable:
- That 81% of Stage III patients would have resectable disease;
  - That the uptake rate of PD-1 inhibitors in BRAF mutant patients would be 74.1% in the adjuvant setting; and
  - That the equivalent number of grandfathered patients to receive a full course of treatment on the PBS would be less than 500 in Year 1 of PBS listing.
- 5.7 The PBAC considered that it would be more appropriate to assume that the proportion of patients who were BRAF mutant positive was 37.7%, which was based on the results of an Australian cohort study by Lyle 2016. In addition, the PBAC considered that the majority of patients would utilise the four weekly dosing schedule and advised that it would be more appropriate to use the estimates provided in the nivolumab flat dosing submission, March 2019 which assumed that 3.0% of patients would receive 3 mg/kg every two weeks, 9.0% would receive 240 mg every two weeks and 88.0% would receive 480 mg every four weeks.
- 5.8 The PBAC considered that the proposal of a RSA consisting of PD-1 inhibitor

subsidisation caps across both the adjuvant and unresectable or metastatic settings, beyond which ■■■% rebates would apply, was appropriate to manage the uncertainty around uptake in the adjuvant setting and changes to use in the unresectable or metastatic setting. To reflect likely expected use in the adjuvant setting the PBAC advised that estimated use should be revised based on the recommendations provided in paragraph 5.7. In terms of adjustments to the current unresectable or metastatic subsidisation caps the PBAC made the following recommendations:

- Assumed growth of the unresectable or metastatic subsidisation caps should be revised from ■■■% to ■■■% per calendar year to more closely align with the incidence of melanoma in Australia (see paragraph 4.26);
- The proportion of BRAF mutant patients should be 37.7%;
- The estimate of first-line PD-1 inhibitor use (either as monotherapy or as nivolumab+ipilimumab) in the unresectable or metastatic setting should be 50% to 60%; rather than 63% to 70% (see paragraph 4.27);
- The proportion of patients who remain recurrence free, which was based on the difference in distant metastases free survival rates at 10 years, should include those who are free of local unresectable recurrence at two to five years. The PBAC recommended that it would be more reasonable to reduce the unresectable or metastatic subsidisation cap by ■■■% to ■■■% from Year 2 onwards (see paragraph 4.31);
- The subsidisation caps should also be reduced to account for patients who recur whilst on, or within six months of completing, adjuvant therapy. The PBAC advised that ■■■% to ■■■% of the unresectable or metastatic PD-1 inhibitor population would be ineligible for further PD-1 inhibitor treatment (see paragraph 4.32).

5.9 The PBAC advised that the above changes to the subsidisation caps in the unresectable or metastatic setting should be made in conjunction with the November 2019 recommendation to extend the listing of NIVO monotherapy and NIVO+IPI to allow first-line use in BRAF mutant patients.

5.10 The PBAC considered that it would be more appropriate for the nivolumab restriction for the adjuvant treatment of melanoma to be split into an initial and continuing phase, as per the current restriction for DAB+TRAM in the adjuvant setting.

5.11 The PBAC considered that adjuvant treatment should not be delayed for post-surgery recovery and should commence within 12 weeks of complete resection.

5.12 The PBAC noted the sponsor's concerns regarding the flow-on restrictions for treatments in the unresectable or metastatic setting and considered that:

- Patients who had received a PD-1 inhibitor as adjuvant therapy and had a recurrence on treatment or within six months of completing treatment should not be able to receive nivolumab+ipilimumab or PD-1 inhibitor monotherapy as first-

line treatment in the unresectable or metastatic setting;

- Treatment should consist of 12 months of active therapy, which could consist of either PBS-subsidised or non-PBS subsidised treatment; and
- Patients who discontinued adjuvant treatment for reasons other than disease progression should not be able to receive the same class of drug first-line in the unresectable or metastatic setting if they had experienced recurrence within six months of discontinuing adjuvant therapy.

- 5.13 The PBAC advised that the flow-on restriction changes for nivolumab, ipilimumab and the BRAF inhibitors should be implemented in conjunction with the restriction changes resulting from the November 2019 recommendation to extend the listings of nivolumab and nivolumab+ipilimumab to allow first-line use in BRAF mutant patients.
- 5.14 The PBAC noted that there would also be flow-on restriction changes to the current PBS listings of pembrolizumab in the unresectable or metastatic setting.
- 5.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for nivolumab:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over placebo in terms of recurrence free survival;
  - b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no medicines for the adjuvant treatment of patients with BRAF wild type melanoma listed on the PBS; and
  - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 5.16 The PBAC recommended that nivolumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 5.17 The PBAC advised that nivolumab is not suitable for prescribing by nurse practitioners.
- 5.18 The PBAC recommended that the Early Supply Rule should not apply to nivolumab.
- 5.19 The PBAC noted that this submission is not eligible for an Independent Review as it was a positive recommendation.

**Outcome:**

Recommended

## **6 Recommended listing**

- 6.1 Amend existing listing as follows:
- Add new indication.

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Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	PBS item code	Proprietary Name and Manufacturer
NIVOLUMAB 40 mg/4 mL injection, 4 mL vial 100 mg/10 mL injection, 10 mg vial	480 mg	5	New (Public) New (Private)	Opdivo® Bristol-Myers Squibb

Restriction Summary [new] / Treatment of concept [new]: Authority Required (telephone)

Concept ID	Category/Program: Section 100 Efficient Funding of Chemotherapy
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction level: <input checked="" type="checkbox"/> Authority Required (Telephone/Emergency/Electronic)
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity: [nil]
	Severity: Resected Stage IIIB, IIIC, IIID or Stage IV
	Condition: malignant melanoma
new	Indication: Resected Stage IIIB, IIIC, IIID or Stage IV malignant melanoma
	Treatment Phase: Initial treatment
24813	Clinical criteria:
24812	The treatment must be adjuvant to complete surgical resection
	AND
10299	Clinical criteria:
10298	Patient must have a WHO performance status of 1 or less
	AND
7890	Clinical criteria:
7889	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
24817	Clinical criteria:
24816	Patient must not have received prior PBS-subsidised treatment for this condition
	AND
24819	Clinical criteria:
24818	The treatment must commence within 12 weeks of complete resection
	AND
new	Clinical criteria: Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy
24451	Prescribing instructions: Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.
14458	Caution: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.

Restriction Summary [new] / Treatment of concept [new]: Authority Required (telephone)

7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.

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new	<b>Indication:</b> Resected Stage IIIB, IIIC, IIID or Stage IV malignant melanoma
	<b>Treatment Phase:</b> Continuing treatment
new	<b>Clinical criteria:</b> Patient must have previously been issued with an authority prescription for this drug for adjuvant treatment following complete surgical resection
	<b>AND</b>
24827	<b>Clinical criteria:</b>
24824	Patient must not have experienced disease recurrence
	<b>AND</b>
new	<b>Clinical criteria:</b> Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy
24451	<b>Prescribing instructions:</b> Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.

**Restriction Summary [new] / Treatment of concept [new]: Authority Required (telephone)**

7606	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised
7607	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply
24811	<b>Indication:</b> Resected Stage IIIB, Stage IIIC or Stage IIID malignant melanoma
	<b>Treatment Phase:</b> Grandfathered treatment
new	<b>Clinical criteria:</b> Patient must have previously received non-PBS subsidised drug for adjuvant treatment following complete surgical resection prior to [1 Month 20XX]
	<b>AND</b>
10299	<b>Clinical criteria:</b>
10298	Patient must have a WHO performance status of 1 or less
	<b>AND</b>
24831	<b>Clinical criteria:</b>
24830	Patient must not have evidence of recurrence
	<b>AND</b>
7890	<b>Clinical criteria:</b>
7889	The treatment must be the sole PBS-subsidised therapy for this condition
	<b>AND</b>
24817	<b>Clinical criteria:</b>
24816	Patient must not have received prior PBS-subsidised treatment for this condition
	<b>AND</b>
new	<b>Clinical criteria:</b> Patient must have commenced non-PBS subsidised treatment within 12 weeks of complete surgical resection, <del>unless delay was necessary due to post surgery</del>
	<b>AND</b>
new	<b>Clinical criteria:</b> Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy
24451	<b>Prescribing instructions:</b> Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.
23701	<b>Prescribing instructions:</b> A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.

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Flow-on changes to DAB+TRAM restrictions in the adjuvant setting:

<b>Dabrafenib</b>	
<b>Schedule:</b>	General
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Category/program:</b>	<input checked="" type="checkbox"/> Authority Required (telephone)
<b>Severity:</b>	Resected Stage IIIB, Stage IIIC or Stage IIID
<b>Condition:</b>	Malignant melanoma
<b>Treatment phase:</b>	Initial treatment
<b>Clinical criteria:</b>	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 Patient must not have received prior PBS-subsidised treatment for this condition.
<b>Treatment criteria:</b>	Treatment must commence within 12 weeks of complete resection, <del>unless delay is necessary due to post-surgery recovery;</del> AND Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma <i>Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy</i>
<b>Notes:</b>	No increase in the maximum quantity or number of units or number of repeats will be authorised.  Special Pricing Arrangements apply.

<b>Dabrafenib</b>	
<b>Schedule:</b>	General
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Category/program</b>	<input checked="" type="checkbox"/> Authority Required (telephone)
<b>Severity:</b>	Resected Stage IIIB, Stage IIIC or Stage IIID
<b>Condition:</b>	Malignant melanoma
<b>Treatment phase:</b>	Continuing treatment
<b>Clinical criteria:</b>	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
<b>Treatment criteria:</b>	<del>Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma</del> <i>Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy</i>
<b>Notes:</b>	No increase in the maximum quantity or number of units or number of repeats will be authorised.  Special Pricing Arrangements apply.

<b>Dabrafenib</b>	
<b>Schedule:</b>	General
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Category/program</b>	<input checked="" type="checkbox"/> Authority Required (telephone)
<b>Severity:</b>	Resected Stage IIIB, Stage IIIC or Stage IIID
<b>Condition:</b>	Malignant melanoma
<b>Treatment phase:</b>	Grandfathered treatment

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<b>Clinical criteria:</b>	<p>Patient must have previously received non-PBS subsidised drug for adjuvant treatment following complete surgical resection prior to [list date]  AND  The condition must be positive for a BRAF V600 mutation  AND  Patient must have a WHO performance status of 1 or less  AND  The patient must not have evidence of recurrence  AND  Patient must be receiving PBS-subsidised trametinib and dabrafenib concomitantly for this condition  AND  Patient must not have received prior PBS-subsidised treatment for this condition.</p>
<b>Treatment criteria:</b>	<p>Non-PBS subsidised treatment must have commenced within 12 weeks of complete surgical resection, <del>unless delay is necessary due to post-surgery recovery,</del>  AND  Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma  <i>Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy</i></p>
<b>Notes:</b>	<p>No increase in the maximum quantity or number of units or number of repeats will be authorised.    Special Pricing Arrangements apply.</p>

<b>Trametinib</b>	
<b>Schedule:</b>	General
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Category/program:</b>	<input checked="" type="checkbox"/> Authority Required (telephone)
<b>Severity:</b>	Resected Stage IIIB, Stage IIIC or Stage IIID
<b>Condition:</b>	Malignant melanoma
<b>Treatment phase:</b>	Initial treatment
<b>Clinical criteria:</b>	<p>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  Patient must not have received prior PBS-subsidised treatment for this condition.</p>
<b>Treatment criteria:</b>	<p>Treatment must commence within 12 weeks of complete resection, <del>unless delay is necessary due to post-surgery recovery;</del>  AND  Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma  <i>Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy</i></p>
<b>Notes:</b>	<p>No increase in the maximum quantity or number of units or number of repeats will be authorised.    Special Pricing Arrangements apply.</p>

<b>Trametinib</b>	
<b>Schedule:</b>	General
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Category/program:</b>	<input checked="" type="checkbox"/> Authority Required (telephone)
<b>Severity:</b>	Resected Stage IIIB, Stage IIIC or Stage IIID
<b>Condition:</b>	Malignant melanoma
<b>Treatment phase:</b>	Continuing treatment

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<b>Clinical criteria:</b>	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
<b>Treatment criteria:</b>	<del>Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma</del> <i>Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy</i>
<b>Notes:</b>	No increase in the maximum quantity or number of units or number of repeats will be authorised. Special Pricing Arrangements apply.

<b>Trametinib</b>	
<b>Schedule:</b>	General
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Category/program:</b>	<input checked="" type="checkbox"/> Authority Required (telephone)
<b>Severity:</b>	Resected Stage IIIB, Stage IIIC or Stage IIID
<b>Condition:</b>	Malignant melanoma
<b>Treatment phase:</b>	Grandfathered treatment
<b>Clinical criteria:</b>	Patient must have previously received non-PBS subsidised drug for adjuvant treatment following complete surgical resection prior to [list date] AND The condition must be positive for a BRAF V600 mutation AND Patient must have a WHO performance status of 1 or less AND The patient must not have evidence of recurrence AND Patient must be receiving PBS-subsidised trametinib and dabrafenib concomitantly for this condition AND Patient must not have received prior PBS-subsidised treatment for this condition.
<b>Treatment criteria:</b>	<del>Non-PBS subsidised treatment must have commenced within 12 weeks of complete surgical resection, unless delay is necessary due to post-surgery recovery,</del> AND <del>Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma</del> <i>Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS subsidised adjuvant therapy</i>
<b>Notes:</b>	No increase in the maximum quantity or number of units or number of repeats will be authorised. Special Pricing Arrangements apply.

For flow-on changes to nivolumab, pembrolizumab and BRAF inhibitor (dabrafenib, vemurafenib; encorafenib recommendation from November 2018) restrictions in unresectable Stage III or Stage IV disease:

- See restrictions in agenda item 7.07 of this meeting.

*These restrictions may be subject to further review. Should there be any changes made to the restrictions the Sponsor will be informed.*

## **7 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **8 Sponsor's Comment**

The sponsor had no comment.