

## **7.12 PEMBROLIZUMAB, Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda<sup>®</sup>, Merck Sharp & Dohme (Australia) Pty Ltd.**

### **1 Purpose of Application**

- 1.1 The minor resubmission sought address the outstanding economic and financial areas of concern relating to the previous submission of pembrolizumab as an adjuvant treatment of patients with completely resected Stage IIIB, IIIC, and IIID melanoma. Major submissions were previously considered by the PBAC in November 2018 and July 2019.

### **2 Background**

#### ***Registration status***

- 2.1 Pembrolizumab was TGA registered on 17 December 2018 for:  
“Monotherapy for the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection.”
- 2.2 A proposal for a six weekly dosing regimen (400 mg every six weeks), as an alternative to the 200 mg every three week regimen, has been submitted to the TGA. The Delegate’s Overview considered that the six weekly dosing regimen was supported in patients with melanoma and as monotherapy in patients with non-small cell lung cancer.
- 2.3 The Sponsor indicated that it is intending to submit a PBAC application to include the six weekly dosing regimen as an alternative to the three weekly regimen for all current and future PBS indications.

#### ***Previous PBAC consideration***

- 2.4 Two major submission for pembrolizumab as an adjuvant melanoma treatment were considered by the PBAC at its November 2018 and July 2019 meetings.
- 2.5 The PBAC has previously considered that pembrolizumab was superior compared to placebo in terms of recurrence free survival but, due to the immaturity of the data (no overall survival data was available), the magnitude of the treatment effect was highly uncertain (paragraph 7.6, Pembrolizumab ratified minutes, July 2019).
- 2.6 The PBAC has previously considered that pembrolizumab was inferior compared to placebo in terms of safety, but that the safety profile was manageable (paragraph 7.8, Pembrolizumab ratified minutes, July 2019).

Public Summary Document – November 2019 PBAC Minutes

2.7 The key issues identified in the July 2019 minutes and how they have been addressed in this minor resubmission are presented below.

**Table 1: Summary of outstanding matters of concern**

Issue identified in July 2019 minutes	How issue was addressed in the November 2019 minor resubmission
<b>Economic issues</b>	
<p>There were a number of concerns with the economic model including:</p> <ul style="list-style-type: none"> <li>• The modelled OS estimates were not only underestimated, but clinically implausible;</li> <li>• The incorporation of external data into the model to estimate transition probabilities due to the immature trial data introduced substantial uncertainty;</li> <li>• The model relied on the surrogate relationship between RFS and OS which remained uncertain; and</li> <li>• The relevance of post-recurrence inputs for the adjuvant PEMBRO arm remained uncertain.</li> </ul> <p>(paragraph 7.10)</p>	<p>The minor resubmission presented cost-minimisation analyses versus:</p> <ul style="list-style-type: none"> <li>• NIVO for all patients; and</li> <li>• DAB+TRAM for BRAF +ve patients.</li> </ul>
<p>The modelled gain in QALYs for PEMBRO versus watchful waiting of 1.03 was highly uncertain given on 0.03 QALYs were accrued during the first 16 months of the model time horizon, the median period for which follow up data from KN054 were available (paragraph 7.11)</p>	
<p>Overall the ICER remained highly uncertain, variable and was most likely underestimated (paragraph 7.12)</p>	
<p>The PBAC considered if NIVO was listed on the PBS for the adjuvant treatment of melanoma, it would be appropriate for PEMBRO to be cost minimised to NIVO; if DAB+TRAM was listed, it would be appropriate for PEMBRO to be cost minimised to DAB+TRAM for the proportion of the population that is BRAF +ve (paragraph 7.13).</p>	
<b>Financial issues</b>	
<p>The financial impact remained high and the average number of administrations per patient (14.01 per year) and the uptake rate (85%) were considered to be overestimations (paragraph 7.14)</p>	<p>The minor resubmission made a number of changes to the July 2019 approach; however, stated that overall, the impact of listing PEMBRO on the PBS would be cost neutral compared to NIVO for all patients and cost neutral compared to DAB+TRAM for BRAF +ve patients.</p>
<p>The PBAC considered that, in the context of the uncertain use across the adjuvant and unresectable or metastatic settings, any proposed RSA should encompass adjuvant and unresectable use of all PD-1 inhibitors. An appropriate RSA would consist of subsidisation caps across both settings, beyond which 100% rebates would apply (paragraph 7.15).</p>	<p>The minor resubmission presented a methodological outline of how RSA subsidisation caps would be calculated.</p>
<p>The subsidisation caps in the unresectable or metastatic setting should include a reduction in utilisation to account for patients receiving adjuvant treatment that results in a cure from the second year onwards (paragraph 7.16)</p>	

DAB+TRAM = dabrafenib + trametinib; ICER = incremental cost effectiveness ratio; NIVO = nivolumab; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PD-1 = programmed cell death-1; PEMBRO = pembrolizumab; QALY = quality adjusted life year; RFS = recurrence free survival; RSA = risk sharing arrangement  
 Source: Compiled during evaluation

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

### 3 Requested listing

- 3.1 The following restrictions were proposed by the Secretariat for pembrolizumab in the adjuvant setting. The PBAC noted that flow-on restriction changes would be required to allow retreatment in the unresectable or metastatic setting for pembrolizumab, nivolumab, ipilimumab, and dabrafenib, vemurafenib and encorafenib (recommended for PBS listing in November 2018) restrictions.
- 3.2 The Secretariat has proposed a listing for pembrolizumab in the adjuvant setting that covers both initial and continuing treatment. Given that pembrolizumab is given as an infusion and treatment should be limited to 12 months, 16 repeats is proposed. The PBAC considered that the listing should be split into initial and continuing to be consistent with the approved restrictions for dabrafenib and trametinib.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
PEMBROLIZUMAB 100 mg/4 mL infusion, 1 x 4 mL vial	200 mg	5 16	Published price: \$9,024.44 (Public hospital) \$9,185.54 (Private hospital)  Effective price: \$TBD (Public hospital) \$TBD (Private hospital)	KEYTRUDA® Merck Sharp & Dohme (Australia) Pty Limited

<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 or IIID
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Resected Stage IIIB, IIIC or IIID malignant melanoma
<b>Restriction level:</b>	<input checked="" type="checkbox"/> Authority Required (Telephone)
<b>Clinical criteria:</b>	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 or IIID melanoma, AND The treatment must not exceed a dose of 200 mg every three weeks.

*Public Summary Document – November 2019 PBAC Minutes*

<b>Notes:</b>	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.
---------------	---

<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 or IIID
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Resected Stage IIIB, IIIC or IIID 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 Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma, AND The treatment must not exceed a dose of 200 mg every three weeks.</p>
<b>Notes:</b>	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.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

## **4 Comparator**

- 4.1 The minor resubmission nominated nivolumab and dabrafenib + trametinib as near-term comparators.
- 4.2 The minor resubmission noted that the PBAC had previously determined pembrolizumab to be non-inferior in terms of efficacy compared to nivolumab and, in BRAF mutant patients, dabrafenib + trametinib (paragraph 7.9, Pembrolizumab ratified minutes, July 2019). The minor resubmission noted that there were differences between the regimens and that they could not be considered directly substitutable.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

## 5 Consideration of the evidence

### ***Sponsor hearing***

5.1 There was no hearing for this item as it was a minor submission.

### ***Consumer comments***

- 5.2 The PBAC noted and welcomed the input from individuals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The individual comments described benefits of treatment with adjuvant pembrolizumab including prolonged life and improved quality of life.
- 5.3 The PBAC noted the advice received from Melanoma Patients Australia which supported the listing of pembrolizumab for Stage IIIB, IIIC and IIID resected melanoma on the PBS.
- 5.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the adjuvant pembrolizumab in Stage III melanoma submission, categorising it as one of the therapies of “highest priority for PBAC listing” on the basis of the Phase III clinical evidence provided by the KN054 trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab, which was a Grade A, which is the highest grade (out of C, and where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies), based on a comparison with placebo in the KN054 trial.<sup>1</sup>

### ***Economic analysis***

- 5.5 The minor resubmission noted paragraph 7.13 of the July 2018 pembrolizumab minutes, which stated “that if nivolumab was listed on the PBS for the adjuvant treatment of melanoma, it would be appropriate for pembrolizumab to be cost minimised to nivolumab....and if dabrafenib + trametinib was listed on the PBS for the adjuvant treatment of BRAF mutant melanoma, it would be appropriate for pembrolizumab to be cost minimised to dabrafenib + trametinib for the proportion of the population that is BRAF mutant positive”.
- 5.6 The minor resubmission therefore presented the following cost minimisation analyses:
- Pembrolizumab versus nivolumab, with and without consideration of treatment duration; and
  - Pembrolizumab versus dabrafenib + trametinib in BRAF mutant patients, with and without consideration of treatment duration.

---

<sup>1</sup> Cherny N, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefits scale, version 1.1. *Annals of Oncology*. 2017; 28: 2340-2366.

- 5.7 Dabrafenib + trametinib was recommended as an adjuvant treatment for BRAF mutant patients in July 2018 and listed on the PBS on 1 November 2019. Nivolumab was deferred in July 2018 and reconsidered by the PBAC in November 2019 for BRAF mutant and BRAF WT patients.

Pembrolizumab versus nivolumab

- 5.8 The equi-effective doses, without consideration of treatment duration (i.e. assuming 12 months treatment for both drugs), nominated in the minor resubmission were:

Pembrolizumab 200 mg Q3W = Nivolumab 480 mg Q4W

- 5.9 The cost minimisation analysis presented below is based on the published price of nivolumab in the unresectable or metastatic setting and includes administration costs.

**Table 2: Cost-minimisation analysis between pembrolizumab and nivolumab (480 mg Q4W), without consideration of treatment duration**

A	AEMP for 480 mg NIVO	4.8 * \$2,076.75	\$9,968.40
B	AEMP for years supply of NIVO	A * 13.04 <sup>a</sup>	\$130,034.22
C	Cost of NIVO administration per year	\$66.10 <sup>b</sup> * 13.04 <sup>a</sup>	\$862.25
<b>D</b>	<b>Cost of NIVO patient per year</b>	<b>B + C</b>	<b>\$130,896.47</b>
E	Dose of PEMBRO	-	200 mg Q3W
F	Yearly dose of PEMBRO	E * 17.39 <sup>c</sup>	3,478.57 mg
G	Cost of PEMBRO administration per year	\$66.10 <sup>b</sup> * 17.39 <sup>c</sup>	\$1,149.67
H	Cost of PEMBRO per year	D – G	\$129,746.80
I	Cost of PEMBRO per mg	H / F	\$37.30/mg
<b>J</b>	<b>Cost minimised AEMP per 100mg vial PEMBRO</b>	<b>I * 100</b>	<b>\$3,729.89</b>
<b>K</b>	<b>Cost of PEMBRO patient (per year)</b>	<b>G + (J * 2 * 17.39<sup>c</sup>)</b>	<b>\$130,896.47</b>

AEMP = approved ex-manufacturer price; MBS = Medicare Benefits Schedule; NIVO = nivolumab; PEMBRO = pembrolizumab; Q3W = every three weeks; Q4W = every four weeks

a 13.04 = 365.25 days per year / 28 day dosing

b MBS item 13915 (100% benefit) – updated from \$65.05 to \$66.10 during evaluation

c 17.39 = 365.25 days per year / 21 day dosing

- 5.10 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 pembrolizumab without consideration of the mean trial treatment durations.

Pembrolizumab versus dabrafenib + trametinib

- 5.11 The equi-effective doses, without consideration of treatment duration (i.e. assuming 12 months treatment for both drugs), nominated in the minor resubmission were:

Pembrolizumab 200 mg Q3W = Dabrafenib 150 mg BD + Trametinib 2 mg OD

- 5.12 The cost minimisation analysis presented below is based on the published prices of dabrafenib and trametinib in the unresectable or metastatic setting and includes administration costs.

**Table 3: Cost-minimisation analysis between pembrolizumab and dabrafenib + trametinib, without consideration of treatment duration**

A	AEMP for 30 day supply of DAB	1* \$8,181.56	\$8,181.56
B	AEMP for 30 day supply of TRAM	1 * \$8,612.17	\$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 * 12.18 <sup>a</sup>	\$204,463.66
E	Cost of testing for BRAF mutation	\$230.95 <sup>b</sup>	\$230.95
<b>F</b>	<b>Cost of DAB+TRAM patient per year</b>	<b>D + E</b>	<b>\$204,694.61</b>
G	Dose of PEMBRO	-	200 mg Q3W
H	Yearly dose of PEMBRO	G * 17.39 <sup>c</sup>	3,478.57 mg
I	Cost of PEMBRO administration per year	\$66.10 <sup>d</sup> * 17.39 <sup>c</sup>	\$1,149.67
J	Cost of PEMBRO per year	F – I	\$203,544.94
K	Cost of PEMBRO per mg	J / H	\$58.51/mg
<b>L</b>	<b>Cost minimised AEMP per 100mg vial PEMBRO</b>	<b>K * 100</b>	<b>\$5,851.39</b>
<b>M</b>	<b>Cost of PEMBRO patient (per year)</b>	<b>G + (J * 2 * 17.39<sup>c</sup>)</b>	<b>\$204,694.61</b>

AEMP = approved ex-manufacturer price; DAB = dabrafenib; MBS = Medicare Benefits Schedule; PEMBRO = pembrolizumab; Q3W = every three weeks; TRAM = trametinib

a 12.18 = 365.25 days per year / 30 day supply

b MBS item 73336 (100% benefit)

c 17.39 = 365.25 days per year / 21 day dosing

d MBS item 13915 (100% benefit) – updated from \$65.05 to \$66.10 during evaluation

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

- 5.13 The minor resubmission stated that the net budget impact of listing pembrolizumab on the PBS/RPBS would be cost neutral compared to nivolumab for all patients and cost neutral compared to dabrafenib + trametinib for all BRAF mutant patients. The minor resubmission stated that this relies on the assumption that nivolumab and dabrafenib + trametinib will be recommended prior to, or at the same time as pembrolizumab. The PBAC considered that the cost-neutrality of pembrolizumab relied on the cost-minimisation analysis with nivolumab.
- 5.14 The minor resubmission used an epidemiological approach to determine the use and cost of pembrolizumab for adjuvant treatment of resected Stage IIIB, IIIC or IIID melanoma. The table below compares the approach taken with that taken in July 2019.

Public Summary Document – November 2019 PBAC Minutes

**Table 4: Comparison of the approaches taken to determine the estimated use and cost of adjuvant pembrolizumab from July 2019 and November 2019**

July 2019 PBAC Resubmission	Approach in current submission
Patients with Stages IIIA > 1mm, IIIB, IIIC and IIID melanoma.	Patients with Stage IIIA melanoma were excluded.
Cost-offsets for adjuvant treatment were calculated by estimating proportions of patients no longer progressing to Stage IV disease. Patient treatment split was based on a market share approach.	As per the approach proposed by PBAC, the current unresectable or metastatic melanoma PD-1 inhibitor RSA was amended to encompass all adjuvant and unresectable PD-1 inhibitor use (para 7.15, Pembrolizumab ratified minutes, July 2019). Direct PD-1 inhibitor offsets were incorporated into this approach.
Estimated eligible patient population was determined by an epidemiological approach without applying proportion estimates for BRAF +ve patients or relative treatment share among classes.	The eligible patient population estimate considers 38% of patients are BRAF +ve (Lyle et al. 2016) and utilised an 80%/20% market share split between the PD-1 inhibitors and DAB+TRAM.
Grandfathered patients were not accounted for as no PAP is currently in place for adjuvant PEMBRO.	1,000 grandfathered patients were included based on the predicted number of patients receiving NIVO via PAPs (para 2.13, nivolumab PSD, March 2019)
Used 1 July 2018 dispensing fees.	Updated.

DAB+TRAM = dabrafenib + trametinib; PAP = patient access program; NIVO = nivolumab; PBAC = Pharmaceutical Benefits Advisory Committee; PD-1 = programmed cell death-1; PEMBRO = pembrolizumab; RSA = risk sharing arrangement

Source: Table 5, p7 of the minor resubmission

- 5.15 A number of changes to the July 2019 approach used to estimate the total population eligible to receive adjuvant treatment of melanoma were made, including: i) the removal of Stage IIIA patients (8.3% of Stage III patients); ii) the removal of a share of BRAF mutant patients who were assumed to have received dabrafenib + trametinib; iii) updated warehoused and grandfathered patient numbers; and iv) average time on treatment was simplified to 14.01 cycles.
- 5.16 The eligible patient population estimate considered that 38% of patients were BRAF mutant and utilised a 80%/20% class share split of the treatment of these patients between PD-1 inhibitors and dabrafenib + trametinib, resulting in 92% of adjuvant patients being treated with a PD-1 inhibitor (i.e. all BRAF wild type (100% \* 62%) + BRAF mutant (80% \* 38%)). The high uptake of PD-1 inhibitor therapy in patients who are BRAF mutant was based on:
- Patients who are BRAF mutant cannot access PD-1 inhibitor therapy as a first-line option in the unresectable or metastatic setting;
  - Clinician feedback stating that there has been a low uptake of dabrafenib + trametinib compared to nivolumab in the adjuvant melanoma patient access programs;
  - The improved safety profile of the PD-1 inhibitors compared to dabrafenib + trametinib;
  - In the unresectable or metastatic setting BRAF mutant patients receive a more durable response with PD-1 inhibitors compared to BRAF/MEK inhibitors (Ugurel et al, 2017). The minor resubmission stated that although similar data are not yet available for adjuvant treatment, it will continue to drive clinician choice.

*Public Summary Document – November 2019 PBAC Minutes*

- 5.17 The PBAC accepted that PD1 inhibitors would generally be preferred over dabrafenib + trametinib in the adjuvant setting for BRAF mutant patients, however considered the assumed 80% market share for the PD1 inhibitors to be an overestimate.
- 5.18 The minor resubmission included 440 warehoused patients (i.e. those who have resection surgery in the 12 weeks prior to PBS listing) and 1,000 grandfathered patients who will be enrolled in the nivolumab patient access program (paragraph 2.13, Nivolumab Public Summary Document, March 2019) as there is no access program for pembrolizumab.
- 5.19 For the financial estimates the minor resubmission utilised an effective dispensed price for maximum amount of \$ [REDACTED].
- 5.20 Cost offsets due to patients no longer requiring treatment in the unresectable or metastatic setting due to cure in the adjuvant setting were applied from Year 2. The PBAC noted cost offsets for patients no longer being eligible to receive treatment in the unresectable setting (due to relapse whilst receiving, or within six months of completing adjuvant treatment) were not considered in the resubmission.
- 5.21 A summary of the net cost to the PBS/RPBS is presented below. The minor resubmission noted that the expected net cost to the PBS/RPBS will be zero, as pembrolizumab would be recommended at the same price per patient as nivolumab. The PBAC noted that the assumptions for the average number of administrations per patient (14.01 per year, based on the KEYNOTE-054 average time on treatment) and the treatment uptake rate of 85% were unchanged from the July 2019 submission. PBAC recalled that it considered that these values were overestimations. The PBAC further considered the number of eligible patients to be overestimated, and the cost offsets to be underestimated. However, the PBAC noted there would be no increase in cost to the PBS/RPBS if pembrolizumab was cost minimised to nivolumab, and pembrolizumab and nivolumab share the same financial expenditure caps through a RSA.

**Table 5: Summary of the net cost to the PBS/RPBS of pembrolizumab**

	2020	2021	2022	2023	2024	2025
Eligible patients	1,801	1,841	1,881	1,920	1,960	2,000
Warehoused/grandfathered	1,440	-	-	-	-	-
Total patients	3,242	1,841	1,881	1,920	1,960	2,000
Total cost	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost offset	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to PBS/RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 8, p12 of the minor resubmission and corrected cost offsets from Tab 5. Impact – net. Att 2 Excel

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 \$90 - \$100 million.

## Risk sharing arrangement

5.22 The minor resubmission proposed a methodology for structuring and calculating the Risk Sharing Arrangement (RSA) and subsidisation caps for the PD-1 inhibitors across the adjuvant and unresectable or metastatic settings as outlined below. Specific calculations were not provided as the sponsor was unaware of the effective adjuvant cost per patient.

**Table 6: Proposed methodology for determining the RSA subsidisation caps**

Step 1	Estimate the effective spend for PD-1 inhibitors in the unresectable or metastatic setting over the next 6 years, with the forecast based on the historical melanoma PD-1 inhibitor growth rate (e.g. 6.5%).
Step 2	Estimate the proportion of adjuvant patients who will receive PD-1 inhibitor therapy versus BRAF/MEK targeted therapy. As outlined above, the minor resubmission estimated that 92% of adjuvant patients would be treated with a PD-1 inhibitor.
Step 3	Estimate the effective spend for PD-1 inhibitors in the adjuvant setting over the next 6 years, based on agreed adjuvant cost per patients and patient numbers from the financial estimates provided above.
Step 4	Calculate the number of patients who will be treated in both the adjuvant and unresectable or metastatic setting (i.e. who receive retreatment). This could be based on the modelled estimates from KN045 (the key pembrolizumab trial) and would consist of patients who received 12 months adjuvant treatment and who remained recurrence free for at least 6 months after completing therapy. The minor resubmission stated that this represents approximately 5% of the PD-1 inhibitor treated adjuvant population.
Step 5	Calculate the offset to the PD-1 inhibitors in the unresectable or metastatic setting by estimating the proportion of adjuvant patients treated who no longer progress to the metastatic setting. The minor resubmission used the modelled estimates from KN054 which were included in the financial estimates provided above from Year 2 onwards. This represented approximately 22% of PD-1 inhibitor treated adjuvant population (0% in Year 1, plateauing at 32% in Year 6).
Step 6	Calculation of subsidisation caps (Sum of Steps 1-4), with rebates paid for any cost to government above these totals.

PD-1 = programmed cell death-1; RSA = Risk Sharing Arrangement  
Source: Text, pp14-15 of the minor resubmission

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## 6 PBAC Outcome

- 6.1 The PBAC deferred making a recommendation regarding the listing of pembrolizumab as adjuvant treatment for patients with completely resected Stage IIIB, IIIC or IIID malignant melanoma. The PBAC considered it appropriate for pembrolizumab to be listed on a cost minimisation basis versus nivolumab, noting that a listing for pembrolizumab would be unable to proceed until a listing was agreed for nivolumab.
- 6.2 The PBAC acknowledged that there was a high clinical need for effective therapies to reduce the risk of recurrence for patients with resected Stage IIIB, IIIC or IIID melanoma. The PBAC acknowledged the consumer comments that described the benefits of treatment with adjuvant pembrolizumab, including prolonged survival and improved quality of life and the strong support from the Medical Oncology Group of Australia.
- 6.3 In terms of the proposed restriction, the PBAC considered that:
- it would be appropriate for the pembrolizumab restriction for the adjuvant

treatment of melanoma to be split into an initial and continuing phase, as per the current restrictions for dabrafenib + trametinib in the adjuvant setting;

- adjuvant treatment should commence within 12 weeks of complete resection; and
- flow-on restrictions would be required for treatments in the unresectable or metastatic setting to allow retreatment.

6.4 The PBAC noted that no new clinical data was presented in the minor resubmission. The PBAC remained satisfied that pembrolizumab was non-inferior in terms of efficacy to nivolumab and, in BRAF mutant patients, dabrafenib + trametinib. The PBAC noted that there was currently limited overall survival data. In terms of safety, the PBAC recalled that it previously considered that nivolumab had a non-inferior profile compared to pembrolizumab in the adjuvant setting, and that both nivolumab and pembrolizumab might be better tolerated than dabrafenib + trametinib.

6.5 The PBAC recalled that it had previously considered that the cost effectiveness model comparing pembrolizumab with routine follow-up appeared to have resulted in an overestimate of the incremental benefits and that the incremental cost effectiveness ratio (ICER) was highly uncertain, variable and most likely underestimated.

6.6 The PBAC recalled that it recommended that if nivolumab was listed on the PBS for the adjuvant treatment of melanoma that it would be appropriate for pembrolizumab to be cost minimised to nivolumab. The PBAC considered that the cost minimisation analysis between pembrolizumab and nivolumab presented in the minor resubmission was appropriate. The PBAC considered that the equi-effective doses were:

Pembrolizumab 200 mg every 3 weeks = Nivolumab 480 mg every 4 weeks

6.7 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.

6.8 The PBAC noted that the derivation of the effective price for pembrolizumab in all adjuvant patients would be reliant on the effective price of nivolumab, which would incorporate both the BRAF mutant and BRAF wild type populations.

6.9 The PBAC considered that if nivolumab was not listed on the PBS, pembrolizumab could be cost minimised to dabrafenib + trametinib in the BRAF mutant population. The equi-effective doses were:

Pembrolizumab 200 mg every 3 weeks =  
Dabrafenib 150 mg twice daily + trametinib 2 mg once daily

6.10 The PBAC noted that the estimated financial implications of listing pembrolizumab on the PBS for use in adjuvant melanoma stated that the net budget impact of listing pembrolizumab on the PBS/RPBS would be cost neutral compared to nivolumab should nivolumab be listed on the PBS for this indication. The PBAC noted that this relied on the assumption that nivolumab would be recommended prior to pembrolizumab, as the cost-neutrality of pembrolizumab relies on the cost

minimisation analysis with nivolumab.

- 6.11 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 100% rebates would apply, was appropriate to manage the uncertainty around uptake in the adjuvant setting and the changes in use in the unresectable or metastatic setting due to patients no longer requiring (due to cure in the adjuvant setting) or no longer being eligible to receive (due to relapse whilst receiving, or within six months of completing adjuvant treatment) treatment.

**Outcome:**

Deferred

## 7 Recommended listing

### Flow-on changes to pembrolizumab restrictions for unresectable Stage III or Stage IV disease

*Amend existing restrictions as follows as a result of the PBAC's November 2019 recommendation for item 4.03 (may be subject to further changes following an outcome for the PBAC's November 2019 deferral of agenda item 7.12; to be implemented at the same time as PBAC's recommendation for item 4.03 of this meeting):*

Initial treatment 1 Restriction Summary 9925 / Treatment of Concept: 9895  
PBS item codes: 10493G (Public) / 10475H (Private)

Concept ID	Category/Program: 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>Restriction level:</b> <input checked="" type="checkbox"/> Authority required - Streamlined (9895)
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
7607	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
25071	<b>Administrative Advice:</b> Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
8676	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
<i>edit</i>	<b>Treatment Phase:</b> Initial treatment 1 – 3 weekly treatment regimen
9245	<b>Clinical criteria:</b>
9244	The condition must be positive for a BRAF V600 mutation
	<b>AND</b>
24933	<b>Clinical criteria:</b>
24871	Patient must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) in the unresectable or metastatic setting unless contraindicated or not tolerated according to the TGA approved Product Information; or
24934	Patient must have experienced disease recurrence whilst receiving a BRAF inhibitor with MEK inhibitor as an adjuvant treatment for resected Stage IIIB, IIIC or IIID melanoma; or
24935	Patient must have experienced disease recurrence within 6 months of completion of adjuvant BRAF inhibitor with MEK inhibitor treatment
	<b>AND</b>
<i>insert NEW</i>	<b>Clinical criteria:</b> Patient must not have been treated with an adjuvant programmed cell death-1 (PD-1) inhibitor for resected Stage IIIB, IIIC, IIID or IV melanoma; or

*Public Summary Document – November 2019 PBAC Minutes*

	<i>Patient must have experienced disease recurrence after at least 6 months from completion of an adjuvant PD-1 inhibitor for resected Stage IIIB, IIIC, IIID or IV melanoma, followed by disease progression after treatment with a BRAF inhibitor (with or without MEK inhibitor) in the unresectable or metastatic setting unless contraindicated or not tolerated according to the TGA approved Product Information</i>
	<b>AND</b>
24876	<b>Clinical criteria:</b>
24875	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma
	<b>AND</b>
7890	<b>Clinical criteria:</b>
7889	The treatment must be the sole PBS-subsidised therapy for this condition
	<b>AND</b>
25069	<b>Clinical criteria:</b>
25068	The treatment must not exceed a total of 6 doses under this restriction
14458	<b>Administrative Advice:</b> 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.

Public Summary Document – November 2019 PBAC Minutes

Initial treatment 2 Restriction Summary 9865 / ToC: 9974  
 PBS item codes: 10493G (Public) / 10475H (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>Restriction level:</b> <input checked="" type="checkbox"/> Authority required - Streamlined (9974)
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
7607	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
25071	<b>Administrative Advice:</b> Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
8676	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
	<b>Treatment Phase:</b> Initial treatment 2 – 3 weekly treatment regimen
16650	<b>Clinical criteria:</b>
16649	The condition must be negative for a BRAF V600 mutation
	<b>AND</b>
18686	<b>Clinical criteria:</b>
<b>Edit</b> 18685	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition <del>the treatment of unresectable Stage III or Stage IV malignant melanoma</del>
	<b>AND</b>
<b>Insert</b> <b>NEW</b>	<b>Clinical criteria:</b> Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment if treated for resected Stage IIIB, IIIC, IIID or IV melanoma
	<b>AND</b>
7890	<b>Clinical criteria:</b>
7889	The treatment must be the sole PBS-subsidised therapy for this condition
	<b>AND</b>
25069	<b>Clinical criteria:</b>
25068	The treatment must not exceed a total of 6 doses under this restriction
14458	<b>Administrative Advice:</b> 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.

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

## 8 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.

## **9 Sponsor's Comment**

MSD is disappointed with the deferral and will continue to work with the PBAC towards a PBS listing for pembrolizumab for eligible adjuvant melanoma patients. More than 60% of patients are BRAF wildtype and currently do not have any treatment options reimbursed in the adjuvant setting.