

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

### 1 Purpose of Application

- 1.1 The submission requested a Section 100 (Streamlined), Efficient Funding of Chemotherapy listing for pembrolizumab as an adjuvant treatment for completely resected Stage III melanoma. Pembrolizumab has not been considered by the PBAC for this indication previously.
- 1.2 The requested listing was based on a cost-utility analysis of pembrolizumab compared with observation (or placebo). The key components of the clinical issues addressed by the submission are summarised below.

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

Component	Description
Population	Patients with completely resected Stage III malignant melanoma
Intervention	Pembrolizumab 200 mg intravenous infusion every 3 weeks, maximum of 18 cycles
Comparator	Main comparator: observation (or placebo) Near-market comparators: <ul style="list-style-type: none"> <li>• Nivolumab</li> <li>• Dabrafenib+trametinib (for BRAF mutation positive patients)</li> </ul>
Outcomes	Primary outcome: recurrence-free survival Secondary outcomes: distant metastasis-free survival, overall survival. Safety: all-cause and treatment-related adverse events
Clinical claim	In patients with resected Stage III melanoma, pembrolizumab is more effective than placebo on the basis of reducing the risk of recurrence, reducing the risk of distant metastases and fewer deaths. In terms of safety, overall, pembrolizumab was well tolerated. Although more adverse events were observed for pembrolizumab compared with placebo, they were manageable and consistent with the safety profile for pembrolizumab in other settings.

Source: Table 1-1, pp11-12 of the submission.

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

### 2 Requested listing

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	Published price:	KEYTRUDA <sup>®</sup> Merck Sharp & Dohme (Australia) Pty Limited
			\$9,023.83 (Public hospital) \$9,187.87 (Private hospital)	
			Effective price:	
			\$ [REDACTED] (Public hospital)	
			\$ [REDACTED] (Private hospital)	

Public Summary Document – November 2018 PBAC Meeting

<b>Category/program</b>	Section 100 (Public/Private), Efficient funding of Chemotherapy
<b>Severity:</b>	Resected Stage III
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Resected Stage III malignant melanoma
<b>Treatment phase:</b>	Initial
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The treatment must be adjuvant to complete surgical resection AND The treatment must be initiated within 13 weeks of surgical resection, unless delay is necessary due to post-surgery recovery AND The treatment must be the sole PBS-subsidised therapy for this condition AND The patient must have a WHO performance status of 0 or 1 AND <i>The patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor for this condition.</i>
<b>Administrative advice</b>	No increase in the maximum quantity or number of units or number of repeats will be authorised.

<b>Category/program</b>	Section 100 (Public/Private), Efficient funding of Chemotherapy
<b>Severity:</b>	Resected Stage III
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Resected Stage III malignant melanoma
<b>Treatment phase:</b>	Continuing
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The patient must have previously been issued with an authority prescription for this drug for this condition in the adjuvant setting AND The treatment must be the sole PBS-subsidised therapy for this condition AND The patient must not have evidence of recurrence AND The total treatment received in the adjuvant setting must not exceed 18 cycles at a dose of 200 mg every 3 weeks
<b>Administrative advice</b>	No increase in the maximum quantity or number of units or number of repeats will be authorised.

<b>Category/program</b>	Section 100 (Public/Private), Efficient funding of Chemotherapy
<b>Severity:</b>	Resected Stage III
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Resected Stage III malignant melanoma
<b>Treatment phase:</b>	Grandfathering
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must have received non-PBS treatment with this drug for this condition in the adjuvant setting prior to [date of PBS listing] AND The treatment must be the sole PBS-subsidised therapy for this condition AND The patient must not have evidence of recurrence AND The total treatment received in the adjuvant setting must not exceed 18 cycles at a dose of 200 mg every 3 weeks
<b>Administrative advice</b>	No increase in the maximum quantity or number of units or number of repeats will be authorised.

- 2.1 The submission proposed a Special Pricing Arrangement (SPA). An SPA applies to the current PBS listing for pembrolizumab for relapsed or refractory classical Hodgkin's lymphoma; however, this does not apply to the listing for unresectable Stage III or Stage IV melanoma. A Risk Sharing Arrangement (RSA), in the form of annual expenditure caps, is shared by the sponsors of pembrolizumab and nivolumab for unresectable Stage III or Stage IV melanoma. The sponsors are required to rebate █% to the Commonwealth for costs exceeding the agreed annual expenditure caps. If pembrolizumab becomes available on the PBS as an adjuvant treatment for completely resected Stage III melanoma, this would likely have downstream consequences for the utilisation of the shared caps for unresectable Stage III or Stage IV malignant melanoma (see paragraphs 6.62 to 6.65 below on the RSA).
- 2.2 The submission stated that retreatment was not being requested within the same adjuvant setting. The ESC noted that the requested PBS restriction for initial adjuvant treatment does not state that patients must not have received prior adjuvant treatment with a programmed cell death-1 (PD-1) inhibitor for this condition. The ESC acknowledged that the efficacy of PD-1 inhibitors in disease that has progressed following prior PD-1 therapy was unknown. The PBAC considered that the criterion, "Patient must not have received prior treatment with a PD-1 inhibitor for this condition" be included in the initial treatment restriction.
- 2.3 The proposed PBS restriction was for patients with resected Stage III malignant melanoma only. Patients with completely resected Stage IV disease were not included in the proposed PBS restriction. The submission of nivolumab adjuvant therapy considered at the July 2018 PBAC meeting was for resectable Stage III or Stage IV melanoma. Both pembrolizumab and nivolumab are currently listed on the PBS for treatment of unresectable Stage III or Stage IV malignant melanoma. The submission interpreted 'unresectable' in the current listing as only applying to Stage III disease, and that all Stage IV patients were eligible for PBS subsidised pembrolizumab regardless of whether or not their disease was resectable. This interpretation was not consistent with the key trials presented in the associated pembrolizumab and nivolumab submissions, which recruited patients with measurable lesion. Therefore, patients with completely resected Stage IV disease would have been excluded from these clinical trials.
- 2.4 The ESC noted that the submission did not present any comparative evidence for the effectiveness and safety of pembrolizumab versus observation (placebo) in the following subsets of patients who would be eligible for PBS-subsidised adjuvant treatment under the requested restriction:
- Patients with Stage IIIA < 1 mm lymph node metastases;
  - Patients with mucosal or ocular melanoma; and
  - Patients who have received prior anti-cancer treatment, other than surgery, for melanoma.

*Public Summary Document – November 2018 PBAC Meeting*

2.5 The submission also requested retreatment with pembrolizumab in unresectable Stage III or Stage IV setting for those patients who have received the full 12 month adjuvant pembrolizumab treatment and remained recurrence free for at least 6 months post the completion of full course of adjuvant treatment. Given that the current listings for pembrolizumab for the treatment of unresectable Stage III or Stage IV melanoma would preclude their use in patients who have previously received pembrolizumab as adjuvant therapy, the following PBS listing was proposed in the submission.

Name, Restriction, Manner of administration and form	Max. Amount (units)	No. of Rpts	Proprietary Name and Manufacturer
PEMBROLIZUMAB 100 mg/4 mL infusion, 1 x 4 mL vial	200 mg	5	KEYTRUDA® Merck Sharp & Dohme (Australia) Pty Limited

<b>Category/program</b>	Section 100 (Public/Private), Efficient funding of Chemotherapy
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition in the unresectable Stage III, or Stage IV setting AND Patient must have completed 12 months of prior therapy with a PD-1 inhibitor for this condition in the resected Stage III setting without a recurrence while on treatment AND Patients must not have experienced a recurrence within 6 months of completing prior therapy with a PD-1 inhibitor in the resected Stage III setting AND The treatment must be the sole PBS-subsidised therapy for this condition AND The patient must have a WHO performance status of 0 or 1
<b>Administrative advice</b>	No increase in the maximum quantity or number of units or number of repeats will be authorised.

2.6 The ESC noted that no comparative evidence was provided to support retreatment with pembrolizumab in the melanoma population and clinical guidelines make no recommendations on retreatment with PD-1 inhibitors.

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

### **3 Background**

### **Registration status**

- 3.1 The submission was made under the TGA/PBAC parallel process and was considered under the Priority Review Pathway. At the time of PBAC consideration, the TGA Delegate’s Overview was available, recommending pembrolizumab for:

“monotherapy for the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection.”

### **Previous PBAC consideration**

- 3.2 This is the first PBAC consideration of pembrolizumab for the proposed indication. A submission requesting the listing of nivolumab as adjuvant therapy for resectable Stage III or Stage IV melanoma was considered at the July 2018 PBAC meeting. The PBAC did not recommend nivolumab for use in these patients as the PBAC considered that the data presented in the submission were immature, the effect on overall survival could not be determined and that the incremental cost-effectiveness ratio was highly uncertain.
- 3.3 Pembrolizumab is currently PBS listed for:
- Unresectable Stage III or Stage IV malignant melanoma who have not received prior treatment with ipilimumab or a PD-1 inhibitor for this condition; and
  - Relapsed or refractory Hodgkin’s lymphoma who have undergone an autologous stem cell transplant (AST) and have experienced relapsed or refractory disease post AST.

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

## **4 Population and disease**

- 4.1 Stage III melanoma includes patients with involvement of regional lymph nodes or the presence of in transit or satellite metastases. Patients who have completely resected Stage III melanoma are at a high risk of developing unresectable disease recurrence, which, in many cases, includes distant metastases. Despite the availability of immunotherapies and targeted therapies for the treatment of advanced/metastatic melanoma, unresectable disease remains associated with high mortality. To reduce the risk of relapse post resection, high-risk patients may be considered candidates for adjuvant treatment.
- 4.2 In Australia, there are no agents currently available on the PBS for adjuvant treatment. Interferon alfa 2b was delisted from the PBS in June 2018 and, as noted in the Cancer Council Australia (CCA) guidelines\*, it is not recommended as standard of care given

---

\* Carlino M, Atkinson V, Long G, et al. What is the role of adjuvant systemic therapy in patients with resected Stage II and Stage III melanoma? Cancer Council Australia; 2018 [updated 13 July 2018]; Available from: [https://wiki.cancer.org.au/australia/Clinical\\_question:What\\_is\\_the\\_role\\_of\\_adjuvant\\_systemic\\_therapy\\_in\\_patients\\_with\\_resected\\_melanoma%3F](https://wiki.cancer.org.au/australia/Clinical_question:What_is_the_role_of_adjuvant_systemic_therapy_in_patients_with_resected_melanoma%3F).

the significant toxicity profile and minimal survival benefits. Therefore, there is an unmet clinical need for these patients.

- 4.3 The CCA guidelines recommend adjuvant treatment of resected Stage III patients with pembrolizumab, nivolumab or dabrafenib+trametinib (DAB+TRAM, only in BRAF positive patients). The guidelines also acknowledge that, currently, patients can only access these treatments if there is eligibility for a clinical trial or through self-funded mechanisms, and observation is the standard of care. If patients develop unresectable Stage III or Stage IV melanoma, they are eligible for PBS-subsidised treatment with targeted therapy or immunotherapy depending on their BRAF mutation status: patients whose tumour expresses BRAF mutations are eligible for BRAF inhibitor ± MEK inhibitor therapy, followed by PD-1 inhibitors upon disease progression; while among those patients with BRAF negative melanoma, PD-1 inhibitors are used as first-line treatment.
- 4.4 If pembrolizumab becomes available on the PBS for use as adjuvant therapy, it is likely to alter subsequent management of recurrent disease, especially the use of PD-1 inhibitors as first- or later-line treatment for unresectable Stage III and Stage IV disease, given that the current listings for pembrolizumab and nivolumab for the treatment of unresectable Stage III or Stage IV melanoma would preclude their use in patients who have previously received PD-1 inhibitors as adjuvant therapy. Although the submission has requested an additional PBS listing for retreatment with pembrolizumab for those who have received the full 12-month course of adjuvant treatment and remained recurrence-free for at least 6 months post completion of the adjuvant treatment, those patients who develop recurrent disease within 18 months post initiation of adjuvant treatment or those who do not complete the full 12-month adjuvant treatment course would be no longer eligible for pembrolizumab (or nivolumab) again in the unresectable setting. The ESC noted that there are no data assessing whether the prior use of pembrolizumab as adjuvant therapy modifies the effectiveness or safety of PD-1 inhibitors when used to treat advanced/metastatic disease.
- 4.5 If the use of pembrolizumab as adjuvant therapy is likely to limit the use of PD-1 inhibitors in treatment of recurrent disease, the PBAC considered that it would be necessary to assess whether the strategy of using pembrolizumab up-front as adjuvant therapy is superior, in terms of effectiveness and cost-effectiveness, to the use of PD-1 inhibitors to treat unresectable disease in patients who experience recurrence in the absence of adjuvant pembrolizumab. The Pre-Sub-Committee Response (PSCR) claimed that adjuvant therapy provided the opportunity to cure melanoma before progression into advanced unresectable stages and that the cost of treating patients increased as the disease progresses. The ESC considered that recurrence-free survival (RFS), the primary outcome in the key trial (KN054), will not capture the effect of differences in later lines of therapy and that overall survival data from a randomised trial comparing these two treatment strategies is required to address this issue, i.e.

earlier versus later line use of pembrolizumab. The ESC noted that overall survival data for the key trial (KN054) is expected to be available in [REDACTED] – see paragraph 6.6.

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

## **5 Comparator**

- 5.1 The submission nominated observation (placebo) as the main comparator. The ESC considered this was reasonable.
- 5.2 The submission also nominated two near-market comparators – nivolumab and DAB+TRAM (for BRAF mutation positive patients). The submission presented indirect comparisons of pembrolizumab with nivolumab and with DAB+TRAM, as there were no head-to-head trials; however, the validity of the evidence was affected by transitivity concerns.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of melanoma, how pembrolizumab would be used in the adjuvant setting, and addressed other matters in response to the Committee’s questions. The clinician noted that the risk of recurrence was greatest in the first two years following resection, with recurrence being unlikely after five years. The clinician considered the aim of adjuvant treatment was to prevent recurrence as RFS correlates with overall survival. The clinician noted that this correlation had been demonstrated in recent trials assessing ipilimumab and BRAF/MEK inhibitors. The clinician considered that retreatment with PD-1 inhibitors in the unresectable setting would be based on individual patient factors; patients whose melanoma recurred during the 12 month period whilst receiving adjuvant pembrolizumab would generally receive an alternative treatment. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (19), health care professionals (4) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pembrolizumab for Stage III melanoma including prolonged life, improved quality of life and fewer side effects.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the pembrolizumab as an adjuvant therapy for 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 (out of C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies which is the highest possible grade and restricted to new curative treatments), based on a comparison with placebo in the Keynote-054 trial.<sup>†</sup>

### **Clinical trials**

- 6.4 The submission was based on one direct randomised controlled trial comparing pembrolizumab with placebo as adjuvant treatment in patients with complete resection of Stage III melanoma: KN054 (N=1,019).
- 6.5 KN054 consists of two parts:
- Part 1: Patients receive their allocated treatment (i.e. pembrolizumab 200mg or placebo) every three weeks for a total of 18 administrations (one year) or until disease recurrence or unacceptable toxicity;
  - Part 2: If a recurrence is documented, patients assigned to the placebo arm in Part 1 are eligible for pembrolizumab if they meet the crossover qualifications specified by the trial protocol (no brain metastases or central nervous system disease, an ECOG status of 0-2 and no second recurrence or progression before enrolment in Part 2). Patients in the pembrolizumab arm are considered for retreatment with pembrolizumab if their disease recurs greater than six months after completing one year of adjuvant pembrolizumab treatment and patients meet the pre-specified rechallenge qualifications (no brain metastases or central nervous system disease, an ECOG status of 0-2 and no second recurrence or progression before enrolment in Part 2). For both crossover and rechallenge, pembrolizumab will be administered every three weeks until progression or recurrence for up to two years.
- 6.6 The available data on Part 1 of the trial were presented in the submission. Part 2 of the trial is currently underway, with only one patient in the pembrolizumab arm having received retreatment at the time of database cut-off. First interim analysis of the retreatment data from Trial KN054 was expected to be available in [REDACTED], with final results in [REDACTED].
- 6.7 Details of the trial presented in the submission are provided in the table below.

---

<sup>†</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.

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

Trial ID	Protocol title/ Publication title	Publication citation
KN054	Adjuvant immunotherapy with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group	March 2018
	Eggermont, A, Blank C, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected Stage III melanoma.	<i>New England Journal of Medicine</i> . 2018; 378:1789-1801
	Study of pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma (MK-3475-054/KEYNOTE-054). NCT02362594	Clinicaltrials.gov June 2018

Source: Table 2-2, p39 of the submission.

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

**Table 3: Key features of the included evidence**

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Used in modelled evaluation?
<b>Pembrolizumab vs. placebo</b>						
KN054	1,019	R, DB <sup>a</sup> , MC 16 months	Low <sup>b</sup>	Completely resected Stage III melanoma <sup>c</sup>	RFS, DMFS <sup>d</sup> , OS <sup>d</sup>	Yes

AJCC = American Joint Committee on Cancer; DB = double blind; DMFS = distant metastasis-free survival; MC = multi-centre; OS = overall survival; R = randomised; RFS = recurrence-free survival.

<sup>a</sup> The treatment arms became un-blinded after first recurrence.

<sup>b</sup> Characteristic adverse events associated with pembrolizumab may result in unmasking the treatment allocation to investigators and patients, therefore safety outcomes and patient-reported outcomes (such as quality of life) may be subject to a moderate to high risk of bias.

<sup>c</sup> Classified using the 7<sup>th</sup> edition of the AJCC melanoma staging system. Patients with Stage IIIA disease were included only if they had metastasis > 1 mm

<sup>d</sup> Data on DMFS and OS were immature for a formal survival analysis. Instead, the submission provided a summary of DMFS and OS events at the October 2017 data cut-off.

Source: Compiled during the evaluation based on Table 2-3, pp42-43, Table 2-4, p45, Table 2-15 and Table 2-16, pp63-4 of the submission.

6.9 The submission was based on data at a median duration of follow-up of 16 months. A 16-month median follow-up was not sufficient for assessment of survival benefits of adjuvant treatment for completely resected Stage III melanoma and was shorter than the follow-up in clinical trials investigating other medicines in the same setting, e.g. minimum of 18 months in Trial Checkmate 238 (nivolumab versus ipilimumab)<sup>‡</sup>; 5.3 years in Trial EORTC 18071 (ipilimumab versus placebo)<sup>§</sup>; and 2.8 years in Trial COMBI-AD (DAB+TRAM versus placebo)<sup>\*\*</sup>.

6.10 RFS was the primary outcome of the key trial KN054. RFS was defined as an episode of recurrence or death. The ESC noted that the most clinically relevant endpoint for evaluation of an anti-cancer medicine is overall survival. The submission referenced a

<sup>‡</sup> Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected Stage III or IV melanoma. *New England Journal of Medicine*. 2017; 377: 1824-1835.

<sup>§</sup> Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in Stage III melanoma with ipilimumab adjuvant therapy. *New England Journal of Medicine*. 2016; 375: 1845-1855.

<sup>\*\*</sup> Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in Stage III BRAF-mutated melanoma. *New England Journal of Medicine*. 2017; 377: 1813-1823.

validation study by Suciu et al<sup>††</sup>, which acknowledged that standard of care has improved markedly since the interferon trials were performed, and that the ongoing evolution of treatment algorithms, including sequential use of new treatment modalities, could weaken the surrogacy of RFS for overall survival, both at the patient and trial levels, as has happened in breast cancer and myeloma. Furthermore, in the interferon trials, post-recurrence treatments were likely to be similar in both the interferon and the placebo arms (i.e. overall survival would not be confounded by subsequent therapies), whereas the use of pembrolizumab as adjuvant therapy is likely to modify the subsequent treatments received by patients with recurrent disease compared to those who do not receive adjuvant PD-1 inhibitor therapy. The ESC considered that:

- the suitability of RFS as a surrogate for overall survival in the assessment of pembrolizumab as adjuvant therapy for resectable Stage III melanoma has not been established; and
- only overall survival data will capture the total impact of listing pembrolizumab as adjuvant therapy for the overall treatment of the target patients.

The ESC advised the further evidence was required to establish the surrogacy relationship, if any, between RFS and overall survival with PD-1 inhibitor therapy, which may also need to be cancer specific. The pre-PBAC Response reiterated the Sponsor's view that there was a surrogate relationship between RFS and overall survival in this setting and provided further evidence. The COMBI-AD trial<sup>‡‡</sup> which compared adjuvant in BRAF/MEK inhibitor therapy (DAB+TRAM) to placebo in patients with BRAF positive Stage III melanoma and based on three years follow-up reported a RFS hazard ratio (HR) of 0.47 and an overall survival HR of 0.57. An indirect comparison of RFS between KN054 and the COMBI-AD trial resulted in a HR of 1.04 (95% confidence interval (CI): 0.72, 1.51). The pre-PBAC Response also provided data from the EORTC 18071 trial<sup>§§</sup> which compared ipilimumab with placebo as an adjuvant treatment for melanoma. A RFS HR of 0.75 resulted in an overall survival HR of 0.72 after five years of follow-up.

- 6.11 The ESC and PBAC noted that patients in KN054 were classified using the 7<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) melanoma staging system, which was introduced in 2007 and has three Stage III subgroups (IIIA, IIIB and IIIC) – see Table 4. Patients are subdivided into prognostic sub-stages depending upon the extent of lymphatic involvement and the characteristics of the primary tumour. The ESC noted that Stage IIIA (7<sup>th</sup> edition) patients were only recruited into KN054 if they had

---

<sup>††</sup> Suciu S, Eggermont A, Lorigan P, et al. Relapse-free survival as a surrogate for overall survival in the evaluation of Stage II-III melanoma adjuvant therapy. *Journal of the National Cancer Institute*. 2018; 110: 87-96.

<sup>‡‡</sup> Long G, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in Stage III BRAF-mutated melanoma. *New England Journal of Medicine*. 2017; 377: 1813-1823.

<sup>§§</sup> Eggermont A, Chiarion-Seleni V, Grob JJ, et al. Prolonged survival in Stage III melanoma with ipilimumab adjuvant therapy. *New England Journal of Medicine*. 2016; 375: 1845-1855.

metastases greater than 1 mm, i.e. those patients with more severe Stage IIIA disease. In addition, although the proportions of patients with each sub-stage of melanoma were comparable between the pembrolizumab and placebo arms, the PBAC noted that the proportion of Stage IIIA patients in KN054 was approximately 16%, compared to 46% for Stage IIIB and 38% for Stage IIIC.

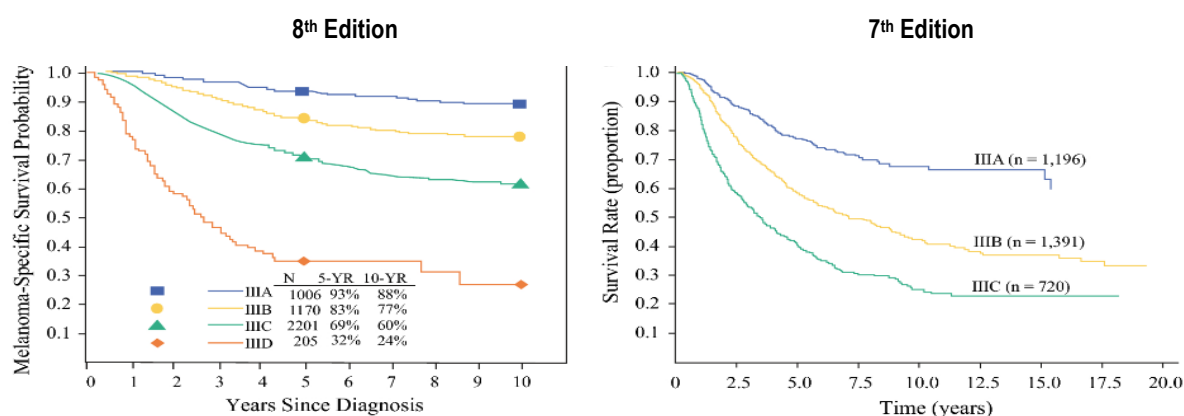
**Table 4: Baseline melanoma stage of patients in the KN054 trial, using the 7<sup>th</sup> edition of the AJCC melanoma staging system**

	Pembrolizumab	Placebo
Participants, n	514	505
Cancer stage, n (%)		
Stage IIIA (metastasis > 1 mm)	80 (15.6%)	80 (15.8%)
Stage IIIB	237 (46.1%)	230 (45.5%)
Stage IIIC (1-3 LN+)	95 (18.5%)	93 (18.4%)
Stage IIIC (≥ 4 LN+)	102 (19.8%)	102 (20.2%)

AJCC = American Joint Committee on Cancer; LN = lymph node  
Source: Table 2-7, pp49-49 of the submission

6.12 From 2017 melanoma has been staged using the 8<sup>th</sup> edition of the melanoma staging system which has four subgroups (IIIA, IIIB, IIIC and IIID). Figure 1 presents a comparison of the survival probabilities for each sub-stage of Stage III melanoma using the 7<sup>th</sup> and 8<sup>th</sup> editions of the AJCC melanoma staging systems.

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



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

6.13 The PBAC noted the limitations associated with comparing different patient cohorts; however, considered that the above comparison suggested that patients in the 8<sup>th</sup> edition cohort had a more favourable survival profile across Stages IIIA, IIIB, and IIIC disease compared with patients with similar stage groupings in the 7<sup>th</sup> edition.

6.14 The PBAC considered that as prognosis varies widely by disease stage, so would the benefit to risk ratio and cost-effectiveness of adjuvant pembrolizumab. The PBAC noted that the proposed listing would allow treatment of Stage III patients regardless

of sub-stage and would include all patients with Stage IIIA disease. In addition, patients, on the basis of the 8<sup>th</sup> edition of the staging system, treated on the PBS would likely have a better prognosis than those treated in KN054, and therefore, the magnitude of benefit from an adjuvant therapy might be lower than seen in the trial. The PBAC noted the submission had not addressed the implications of this difference on the likely cost-effectiveness of pembrolizumab for adjuvant treatment. The PBAC considered the appropriate patient population for treatment was unclear.

### Comparative effectiveness

6.15 RFS results of the intention-to-treat population in Trial KN054 are presented in Table 5 and Figure 2 below.

**Table 5: Results of recurrence-free survival from Trial KN054 (ITT population)**

	<b>Pembrolizumab N=514</b>	<b>Placebo N=505</b>	<b>Absolute difference<sup>a</sup></b>	<b>HR<sup>a</sup> (98.4% CI) p-value (log rank)</b>
Events, n (%)	135 (26.3%)	216 (42.8%)	-16.5%	–
Loco-regional recurrence only	55 (10.7%)	77 (15.2%)	-4.5%	–
Distant metastasis only	69 (13.4%)	114 (22.6%)	-9.2%	–
Loco-regional and distant <sup>b</sup>	9 (1.8%)	24 (4.8%)	-3.0%	–
Death	2 (0.4%)	1 (0.2%)	0.2%	–
Median RFS (95% CI), months	NR	20.4 (16.2, NR)	–	0.57 (0.43, 0.74) p < 0.0001
RFS (95% CI), %				
6 months	82.2 (78.6, 85.3)	73.3 (69.2, 77.0)	8.9%	–
12 months	75.4 (71.3, 78.9)	61.0 (56.5, 65.1)	14.4%	–
18 months	71.4 (66.8, 75.4)	53.2 (47.9, 58.2)	18.2%	–

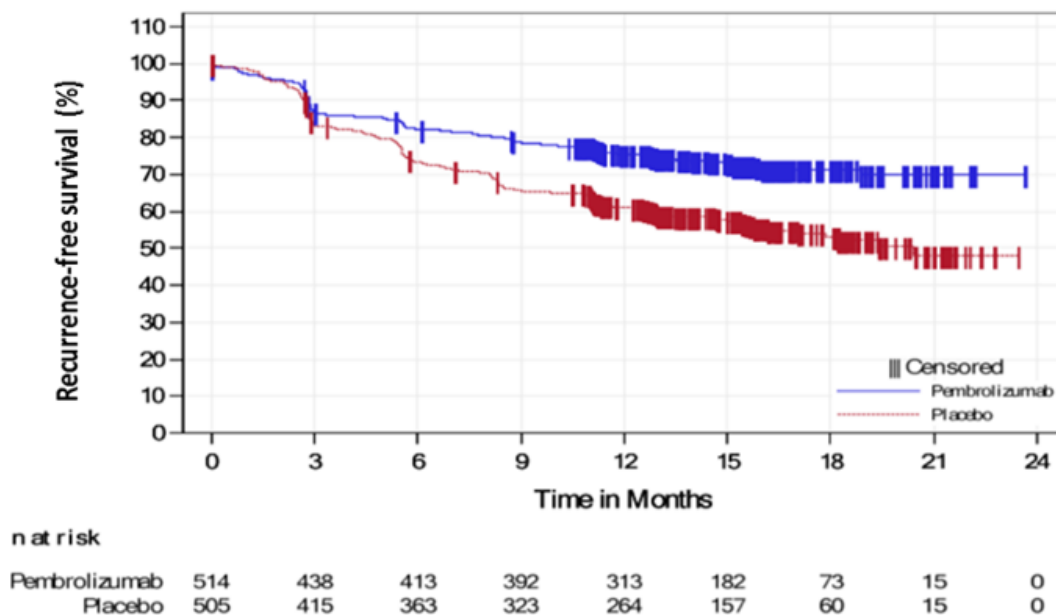
CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NR = not reached; RFS = recurrence-free survival

<sup>a</sup> Pembrolizumab vs Placebo

<sup>b</sup> Diagnosed within 30 days of each other

Source: Table 2-20, p73 of the submission

Figure 2: Kaplan Meier plot for recurrence-free survival from Trial KN054 (ITT population)



ITT = intention-to-treat

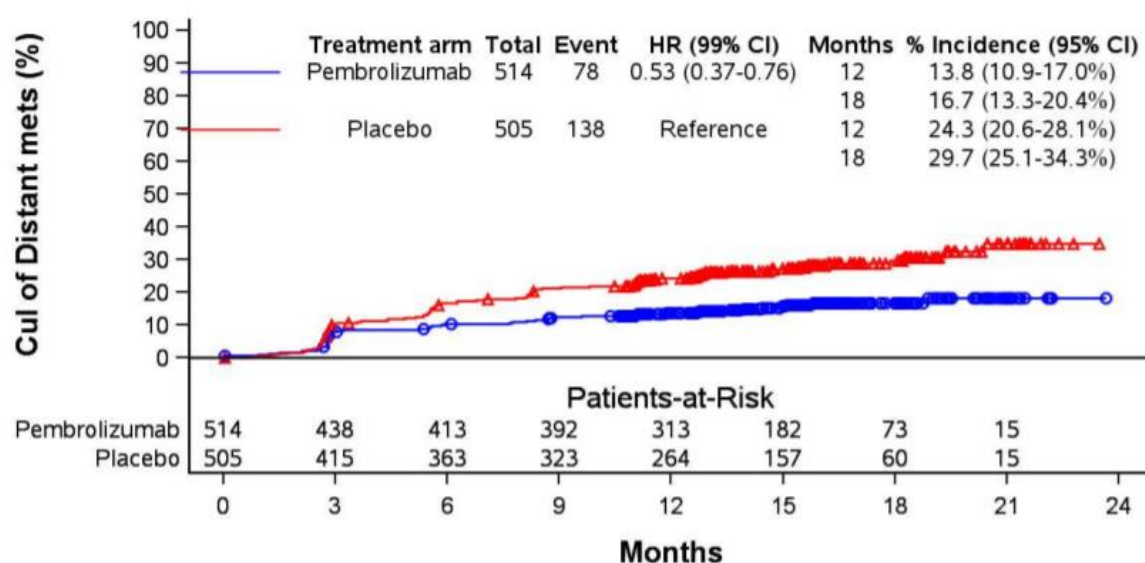
Source: Figure 2-4, p73 of the submission

- 6.16 With a median follow-up of 16.0 months for both treatment arms, a total of 351 patients had a first recurrence of disease or died: 135 (26.3%) in the pembrolizumab group and 216 (42.8%) in the placebo group. Pembrolizumab as adjuvant therapy for treatment of resected Stage III melanoma was associated with a statistically significant reduction in risk of recurrence or death compared with placebo (HR = 0.57; 98.4% CI: 0.43, 0.74). The RFS was 71.4% at 18 months for pembrolizumab and 53.2% in the placebo treatment arm.
- 6.17 The PBAC noted that visual inspection of the Kaplan-Meier curves for RFS suggests that the relative treatment effect was not constant over time. The curves initially overlying each other before diverging at approximately Month 3 (the first scheduled imaging assessment). If the proportional hazards assumption does not hold, the estimated HR, as a measure of the relative treatment effect, may be unreliable given the measure's dependency on follow-up time. The possible extent and direction of any bias arising from this issue was unclear.
- 6.18 The ESC and PBAC noted that RFS data in Trial KN054 were immature. The median RFS was not reached in the pembrolizumab arm. Therefore, the absolute magnitude of the treatment effect, in terms of the difference in median RFS between the treatment groups, could not be determined. It was noted that although the difference in RFS event rates between the two treatment arms had reached statistical significance, it was unknown whether the magnitude of the difference would remain unchanged with a longer follow-up. The PBAC has previously noted that hazard ratios for overall survival tend to become less favourable over time (Paragraph 7.7, Nivolumab Public

Summary Document (PSD), July 2016 PBAC Meeting). The extent of the potential for bias arising from the immaturity of the RFS data was unclear.

- 6.19 The above RFS data were from one pre-specified interim analysis based on trial protocol for KN054. As the superiority threshold was met for RFS after the pre-specified interim analysis, this is now considered the final RFS analysis.
- 6.20 The PSCR presented the 18-month cumulative incidence of distant metastasis (see Figure 3).

Figure 3: Cumulative incidence of distant metastasis (alone or combined with loco-regional) as first type of recurrence



CI = confidence interval; Cul = cumulative incidence; HR = hazard ratio  
 Source: Figure 1, p5 of the PSCR

- 6.21 After 18 months, patients treated with pembrolizumab were less likely to develop distant metastases compared to patients on placebo (HR = 0.53; 99% CI: 0.37, 0.76).
- 6.22 At the data cut-off, a total of [REDACTED] patients had died, with the mortality rate lower in the pembrolizumab arm than in the placebo arm ([REDACTED]% vs [REDACTED]%). Given the immaturity of the data (only [REDACTED]% of patients had died), the PBAC considered that no conclusion could be drawn regarding the overall survival benefits associated with pembrolizumab adjuvant therapy for treatment of completely resected Stage III melanoma. The final survival analysis will be undertaken after reaching 380 deaths as pre-specified in the trial protocol, which was expected to be in [REDACTED].
- 6.23 Although quality of life data derived from KN054 were used in the modelled economic evaluation, the submission did not provide any detail on the quality of life data analysis.

## Comparative harms

6.24 The key adverse events in Trial KN054 are summarised below.

Table 6: Summary of key adverse events in Trial KN054 (as treated population<sup>a</sup>)

	Pembrolizumab N=509	Placebo N=502	Risk difference (95% CI)	Relative risk (95% CI)
<b>All-cause AEs, n (%)</b>				
Any grade	475 (93.3%)	453 (90.2%)	0.03 (-0.00, 0.06)	1.03 (1.00, 1.07)
Grade 3-5	158 (31.0%)	96 (19.1%)	<b>0.12 (0.07, 0.17)</b>	<b>1.62 (1.30, 2.03)</b>
<b>Treatment-related AEs, n (%)</b>				
Any grade	396 (77.8%)	332 (66.1%)	<b>0.12 (0.06, 0.17)</b>	<b>1.18 (1.09, 1.27)</b>
Grade 3-5	74 (14.5%)	17 (3.4%)	<b>0.11 (0.08, 0.15)</b>	<b>4.29 (2.57, 7.17)</b>
AEs leading to discontinuation	62 (12.2%)	8 (1.6%)	<b>0.11 (0.08, 0.14)</b>	<b>7.64 (3.70, 15.8)</b>
Death	1 (0.2%)	0	0.00 (-0.00, 0.01)	–
<b>Most frequent treatment-related AEs, Grade 3-5 (≥ 1% of patients in either arm)</b>				
Colitis	6 (1.2%)	0	0.01 (0.00, 0.02)	–
Type 1 diabetes	5 (1.0%)	0	0.01 (0.00, 0.02)	–
Diarrhoea	4 (0.8%)	3 (0.6%)	0.00 (-0.01, 0.01)	1.31 (0.30, 5.85)
<b>Adverse events of special interest (AEOSI)<sup>b</sup></b>				
Any grade	173 (34.0%)	38 (7.6%)	<b>0.26 (0.22, 0.31)</b>	<b>4.49 (3.23, 6.24)</b>
Treatment-related	162 (31.8%)	28 (5.6%)	<b>0.26 (0.22, 0.31)</b>	<b>5.71 (3.90, 8.36)</b>
Grade 3-5	36 (7.1%)	3 (0.6%)	<b>0.06 (0.04, 0.09)</b>	<b>11.83 (3.67, 38.18)</b>
Leading to discontinuation	33 (6.5%)	6 (1.2%)	<b>0.05 (0.03, 0.08)</b>	<b>5.42 (2.29, 12.83)</b>
Death	0	0	0.00	–
<b>Frequent AEOSI, any grade (≥ 1% of patients in either arm)<sup>b</sup></b>				
Hypothyroidism	75 (14.7%)	14 (2.8%)	<b>0.12 (0.09, 0.15)</b>	<b>5.28 (3.03, 9.22)</b>
Hyperthyroidism	53 (10.4%)	6 (1.2%)	<b>0.09 (0.06, 0.12)</b>	<b>8.71 (3.78, 20.08)</b>
Pneumonitis	16 (3.1%)	3 (0.6%)	<b>0.03 (0.01, 0.04)</b>	<b>5.26 (1.54, 17.94)</b>
Thyroiditis	12 (2.4%)	0	<b>0.02 (0.01, 0.04)</b>	–
Colitis	13 (2.6%)	2 (0.4%)	<b>0.02 (0.01, 0.04)</b>	<b>6.41 (1.45, 28.26)</b>
Hypophysitis	8 (1.6%)	0	<b>0.02 (0.00, 0.03)</b>	–
Sarcoidosis	7 (1.4%)	0	<b>0.01 (0.00, 0.02)</b>	–
Hepatitis	6 (1.2%)	1 (0.2%)	0.01 (0, 0.02)	5.92 (0.71, 48.98)

Note: Statistically significant results are bolded

AE = adverse events; AEOSI = adverse event of special interest; CI = confidence interval

<sup>a</sup> A total of 8 randomised subjects did not receive treatment with either pembrolizumab or placebo. Five subjects randomised to pembrolizumab did not receive treatment due to subject withdrawal (3 subjects), ineligibility due to brain metastasis (1 subject), and other reason (1 subject). Three subjects randomised to placebo did not receive treatment due to subject withdrawal (2 subjects) and progressive disease (1 subject).

<sup>b</sup> Risk differences and relative risks for AEOSI were calculated during the evaluation, using Stata v14.2

Source: Table 2-24, p78, Table 2-25, pp79-80, and Table 2-47, p97 of the submission; Table 12-12, p66 of the KN054 clinical study report of the submission.

- 6.25 The occurrence of all-cause adverse events, treatment-related adverse events, treatment-related Grade 3-5 adverse events, and adverse events leading to discontinuation were consistently higher in patients receiving pembrolizumab than in the placebo patients, although the differences were not always statistically significant.
- 6.26 In KN054, adverse events of special interest were defined as immune-mediated events and infusion-related reactions considered to be risks or potential risks specifically identified for pembrolizumab. More patients in the pembrolizumab arm experienced adverse events of special interest than in the placebo group (173 (34.0%) versus 38 (7.6%)). Most were Grade 1 or 2 in severity and were treatment-related. The most frequently reported events of special interest (any grade) were hypothyroidism (14.7%), hyperthyroidism (10.4%), pneumonitis (3.1%), colitis (2.6%) and thyroiditis (2.4%). These events were reported in a statistically significantly higher proportion of patients in the pembrolizumab group than in the placebo group.
- 6.27 Overall, the adverse events of special interest reported in KN054 were consistent with the immune-associated adverse events in other pembrolizumab trials for different indications. No new safety signals were identified.

### Benefits/harms

- 6.28 A summary of the comparative benefits and harms for pembrolizumab versus placebo is presented in the table below.

**Table 7: Summary of comparative benefits and harms for pembrolizumab and placebo**

<b>Benefits</b>						
RFS: Trial KN054 <sup>a</sup>						
	Pembrolizumab	Placebo	Absolute difference	Relative risk	HR (98.4% CI)	
Recurrence or death events, n/N (%)	135/514 (26.3%)	216/505 (42.8%)	-16.5%	0.614	–	
Median RFS, months	NR	20.4 (16.2, –)	–	–	0.57 (0.43, 0.74)	
<b>Harms</b>						
AEs: Trial KN054 <sup>a</sup>						
	Pembrolizumab n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Pembrolizumab	Placebo	
Grade 3-5 AE	158/509	96/502	1.62 (1.30, 2.03)	31.0	19.1	0.12 (0.07, 0.17)
TR-AE leading to discontinuation <sup>a</sup>	62/509	8/502	7.64 (3.70, 15.8)	12.2	1.6	0.11 (0.08, 0.14)
Treatment-related Grade 3-5 AEOSI <sup>a</sup>	36/509	3/502	11.83 (3.67, 38.18)	7.1	0.6	0.06 (0.04, 0.09)

AE = adverse events AEOSI = adverse event of special interest; CI = confidence interval; HR = hazard ratio; NR = not reached; RD = risk difference; RFS = recurrence-free survival; RR = relative risk; TR-AE = treatment-related adverse event

<sup>a</sup> Median duration of follow-up 16 months

Source: Table 2-20, p73, Table 2-24, p78 and Table 2-25, pp79-80 of the submission; Table 12-12, p66 of the KN054 clinical study report.

- 6.29 On the basis of evidence presented by the submission, for every 100 patients treated with pembrolizumab in comparison to placebo and over a median duration of follow-up of 16 months:

- Approximately 17 more patients remained recurrence-free. However, it is currently unknown if this will impact on patient's overall survival.
- Approximately 12 additional patients would experience a Grade 3-5 all-cause adverse event.
- Approximately 11 additional patients would experience a treatment-related adverse event leading to discontinuation.
- Approximately 6 additional patients would experience a treatment-related Grade 3-5 adverse event of special interest.

### ***Clinical claim***

- 6.30 The submission described pembrolizumab as superior in terms of effectiveness compared with placebo and as well tolerated.
- 6.31 The PBAC considered that the submission's claim that pembrolizumab was superior to placebo in terms of RFS for treatment of completely resected Stage III malignant melanoma was reasonable, based on the interim analysis from Trial KN054. The PBAC noted that the magnitude of the RFS benefits associated with pembrolizumab could not be reliably determined due to the immaturity of the RFS data.
- 6.32 The PBAC noted that the magnitude of RFS benefit for patients with Stage IIIA (metastases greater than 1 mm) should be considered highly uncertain due to the small proportion of patients with this sub-stage of disease recruited into the trial.
- 6.33 The PBAC noted that no formal analysis could be performed for overall survival as a small number of death events (██████████%) occurred during the observation period of the trial. The validity of surrogacy of RFS for overall survival remained uncertain.
- 6.34 The PBAC noted that the submission did not make a clinical claim, in terms of safety, for pembrolizumab in comparison with the main comparator, placebo. The PBAC considered pembrolizumab was inferior to placebo in term of safety.

### ***Economic analysis***

- 6.35 The submission presented a modelled economic evaluation based on KN054 and data from a range of literature. The type of economic evaluation presented was a cost-utility analysis. The model structure and rationale are summarised below.

**Table 8: Summary of model structure and rationale**

Component	Summary
Time horizon	10 years in the model base case versus 16 months in the KN054 trial
Outcomes	LYG and QALYs
Methods used to generate results	Markov cohort model
Health states	Four health states: Recurrence-free (RF); Locoregional recurrence (LR); Distant metastases (DM); Death
Cycle length	1 week
Transition probabilities	<ul style="list-style-type: none"> <li>• Probabilities for transitions from RF health state were based on parametric function curves derived by fitting parametric functions to the observed trial data. Trial data were not directly used in the model.</li> <li>• Transition probabilities from LR to DM were based on Flatiron database, from LR to death were based on KN054 and extrapolated beyond trial duration, or background mortality, whichever is greater;</li> <li>• Transition probabilities from DM to death were based on KN006 trial for those who received pembrolizumab in the advanced setting and a network meta-analysis of trials of other first-line treatments for patients who receive anti-cancer treatments other than pembrolizumab. Exponential models of OS and PFS were used for extrapolation.</li> <li>• The submission assumed that transition probabilities from LR to either DM or death were the same for both pembrolizumab and observation adjuvant treatment arms.</li> <li>• For each adjuvant treatment arm, the transition probability from DM to death depended on the first-line treatments received for advanced melanoma.</li> </ul>

DM = distant metastases; LR = locoregional recurrence; LYG = life years gained; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; RF = recurrence-free

Source: Compiled during the evaluation based on information presented in Section 3 of the submission.

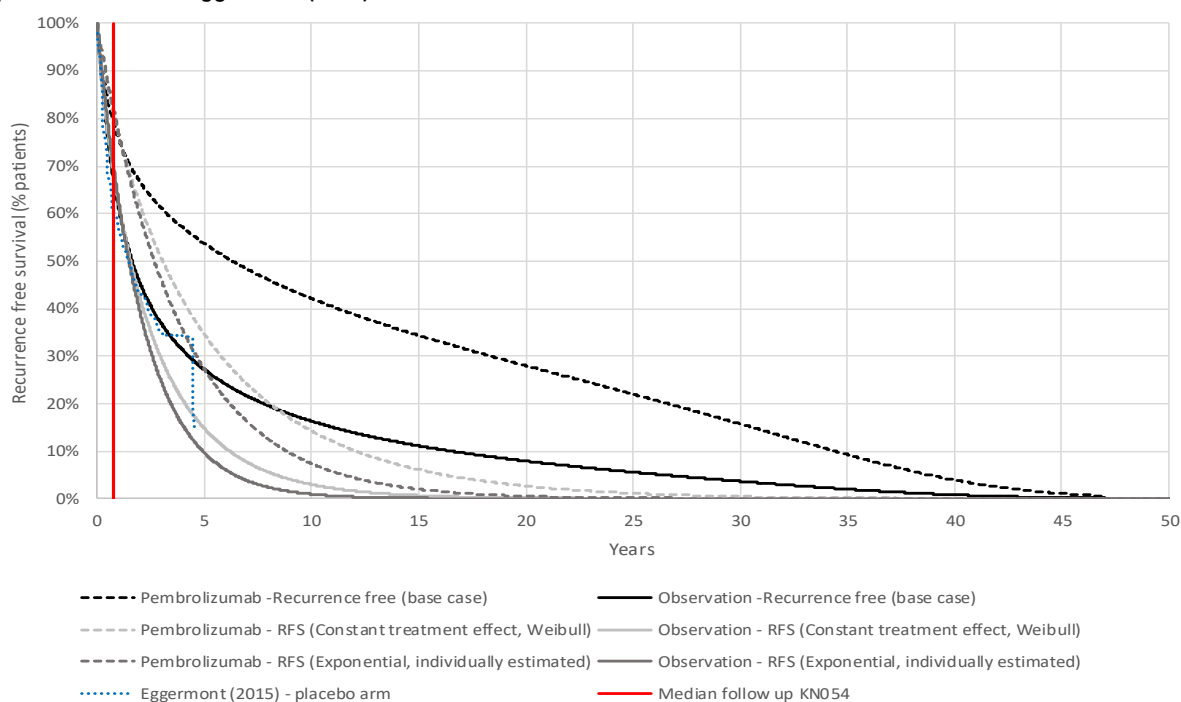
6.36 The population of the model was assumed to be the same as that in the KN054 trial. However, the trial population may not be representative of the population for whom the PBS listing is sought, in terms of disease severity. The PBAC noted that approximately 84% of patients recruited to the trial had either Stage IIIB or IIIC melanoma, classified using the 7<sup>th</sup> edition of the AJCC melanoma staging system. The PBAC were concerned that the model population was therefore representative of patients with more severe late stage disease and that this had implications when assessing the cost-effectiveness of adjuvant pembrolizumab in patients with earlier stage and less severe melanoma (i.e. Stages IIIA and IIIB, using the 8<sup>th</sup> edition of the AJCC melanoma staging system).

6.37 In the distant metastases (DM) health state, progressions to death were based on:

- The expected market share of subsequent therapies. For the observation arm, these were based on the DUSC Melanoma Report (2018). In the adjuvant pembrolizumab arm, the market share differed based on whether patients would be eligible for retreatment with pembrolizumab.
- PFS and overall survival estimates for first-line pembrolizumab in the unresectable setting were derived from the PFS and overall survival curves from KN006, using an exponential parametric function. KN006 is a pembrolizumab trial in the first-line setting for the treatment of unresectable melanoma.

- 6.38 The hazard ratios for PFS and overall survival for each of the advanced treatments in comparison with pembrolizumab were derived from a network meta-analysis. The submission did not discuss potential limitations with these indirect comparisons in terms of the transitivity of the trials, nor whether the proportional hazards assumptions held. The PSCR provided more information on the network meta-analysis to address these concerns. None of the patients in these studies received adjuvant pembrolizumab, and therefore would not be representative of a population who have received pembrolizumab treatment in the adjuvant setting. The PSCR stated that in the modelled base case, patients were not eligible to receive pembrolizumab in the advanced setting unless they completed the adjuvant course (12 months) and remained recurrence-free for an additional six months. Those who recurred earlier than 18 months were not eligible to receive a PD-1 inhibitor.
- 6.39 The modelled RFS data were based on immature trial evidence. At a median duration of follow-up of 16 months, the majority of patients in each arm remained in the recurrence-free (RF) health state. The ESC considered that the predicted profiles for recurrence appeared favourable to the adjuvant pembrolizumab arm, showing a substantial difference (25.8%) in recurrence survival rate at 10 years (the time horizon of the model) between the two arms (i.e. at 10 years the modelled RFS of 16.3% in the observation arm vs 42.1% in the adjuvant pembrolizumab arm). The ESC considered that the magnitude of treatment effect remains uncertain given the short duration of follow up in KN054 (16 months).
- 6.40 Figure 4 compares the base case selected for RFS with other parametric functions. In addition, data from the placebo arm of Eggermont et al, 2015 (which compared ipilimumab to placebo and had a median follow up of 5.3 years) was included. This provided a comparison with the RFS function in the observation arm of the model.

Figure 4: Parametric survival functions for RFS used in the base case and sensitivity analysis and compared with the placebo arm from Eggermont (2015)<sup>\*\*\*</sup>



DM = distant metastases; LF = locoregional; RF = recurrence-free; RFS = recurrence-free survival

Note: The time horizon of the submission's base case was 10 years. The base case model used parametric models (RF → LR recurrence = Gompertz; RF → DM = generalised gamma) fitted individually to each treatment arm.

The sensitivity analysis described as 'Constant treatment-effect' used parametric models (Weibull for both RF → LR recurrence and RF → DM) that incorporated a time-constant treatment effect.

The sensitivity analysis described as 'Exponential, individually estimated' referred to the sensitivity analysis conducted by the submission (Section 3.9) where exponential parametric functions were individually fitted to the RF → LR recurrence and RF → DM in each of the adjuvant treatment arms.

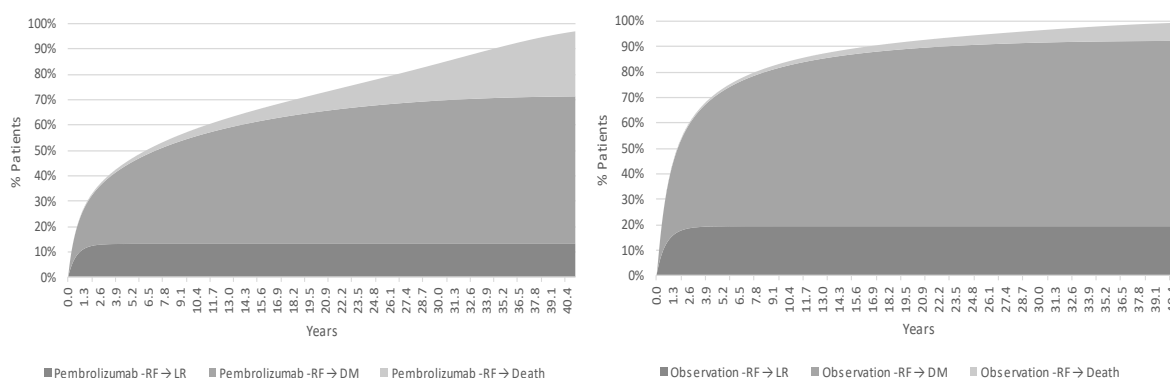
Source: Compiled during the evaluation based on information presented in Att 18 CEM.xlsx

6.41 In order to fit parametric models to each of the individual health state transitions (RF to locoregional (LR) recurrence and RF to DM), standard survival-analysis methods were used with one modification to account for competing risks: when analysing time to each specific type of RFS failure; the two competing failure types were treated as censoring events. The submission selected the Gompertz function for RF to LR recurrence and the generalised gamma function for RF to DM. The ESC noted that the fit of alternative parametric curves to the transitions were not presented. Different parametric functions were tested in the sensitivity analyses.

<sup>\*\*\*</sup> Eggermont A, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk Stage III melanoma (EORTC 18071): A randomised, double-blind, phase 3 trial. *The Lancet Oncology*. 2015; 16(5): 522-530.

6.42 The majority of RFS failures were due to distant metastases, with a much smaller proportion of patients experiencing a locoregional recurrence. It was noted that the parametric functions used to estimate the transition probabilities from the RF health state resulted in very few patients transitioning to the LR recurrence health state after approximately 2 years – see Figure 5.

Figure 5: Cumulative incidence of each RFS failure type – Left panel: pembrolizumab arm; Right panel: observation arm



DM = distant metastases; LR = locoregional; RF = recurrence-free; RFS = recurrence-free survival

Source: Compiled during the evaluation based on information presented in 'Trace\_AdjReg1' sheet in 'Att 18 CEM.xlsx' and 'Trace\_AdjReg2' sheet in 'Att 18 CEM.xlsx'

6.43 The ESC noted that distant metastases free survival (DMFS) was a composite of RF to LR, LR to DM and RF to DM. As there was limited trial data to estimate LR to DM transitions, external data from the Flatiron database was used. The submission fitted an exponential parametric function to observed data on time to distant metastases from the time of entry into the LR state, resulting in an equivalent annual probability of 0.365 of moving from LR to DM being applied to both treatment arms.

6.44 The PBAC noted that the modelled overall survival in both the pembrolizumab (█████% at 5 years and █████% at 10 years) and placebo (█████% at 5 years and █████% at 10 years) arms were low when compared to survival rates presented in the 8<sup>th</sup> edition of the AJCC Staging Manual, which estimated five- and 10-year melanoma specific survival probabilities of 77% and 69% respectively for all Stage III patients.

6.45 Utilities for RF, LR and DM (pre-progression) health states (see Table 9 below) were derived from KN054. The submission did not provide adequate information to assess the appropriateness of these estimates. Response rates to the EQ-5D-3L questionnaires at each of the nominated follow up points were not provided. Therefore it is unknown whether the data were derived from a representative sample of the trial population. Further analyses of the risk of bias associated with lost to follow up and its relationship to the timing of the data collection would be helpful. Utilities for DM (post-progression) were based on Beusterien et al, 2009. The model was not particularly sensitive to the utility values used. The ESC noted that the utility value for

DM (post-progression) from Beusterien et al, 2009 was considerably lower than the value used in the March 2016 submission for progression in unresectable Stage III/IV disease (see Table 8). A sensitivity analysis incorporating the utility values from March 2016 resulted in an ICER of \$15,000/QALY - \$45,000/QALY. The pre-PBAC Response noted that the utility weights for RF, LR and pre-progression DM were derived from EQ-5D-3L questionnaires completed in KN-054 between baseline (n = 1,011) and week 48 (n = 652), with compliance ranging from 88.4% to 93.4%. As there were inadequate patient numbers at post-progression DM to inform the model, a literature-based estimate was used.

**Table 9: Utility values applied in the model**

Health state	Utility values applied in November 2018 submission for resected Stage III disease	Utility values applied in March 2016 submission for unresectable Stage III/IV disease
Recurrence-free (without toxicity)	0.85	0.85
Locoregional recurrence	0.85	0.85
Distant metastases (pre-progression)	0.85	0.85
Distant metastases (post-progression)	0.85	0.85

Source: Table 3-12, p33 of the submission and March 2015 submission for pembrolizumab

- 6.46 The submission stated that most of the treatments used in the advanced setting (i.e. unresectable melanoma) were subject to SPAs. Therefore, in the base case a 10% discount was applied to the published ex-manufacturer prices across all advanced treatments, with 10% discount applied to the MEK inhibitors used in combination with BRAF inhibitors to provide an effective price for the combination that is marginally higher than the BRAF inhibitors as monotherapy.
- 6.47 The cost of subsequent therapies in the advanced setting for unresectable melanoma contributed substantially to the cost offsets, reducing the total incremental costs of pembrolizumab over observation. The duration of the subsequent treatments and the proportions of patients receiving subsequent treatments in each arm are uncertain:
- The duration of first-line treatments in advanced unresectable melanoma was based on their respective PFS curves (derived from KN006 and network meta-analysis for other first-line treatments) and extrapolated using an exponential function. The PSCR stated that the exponential distribution was the only appropriate form and that other forms would require assessment of how long patients had been in the distant metastases health state, making the model significantly more complex. The ESC considered that use of the PFS in longer-term clinical trials would likely favour pembrolizumab, as PFS is generally the maximum time on treatment. The pre-PBAC Response disagreed, stating that time on treatment was not expected to underestimate treatment costs, as a treat until progression approach was consistent with the PBS criteria;
  - The model assumed that all patients entering DM state would be eligible for further treatments. Given that there were a larger proportion of patients entering DM state in the placebo arm (82%) than in the adjuvant pembrolizumab arm (55%) during the modelled time horizon, there were greater costs of subsequent therapies in the

observation arm than in the adjuvant pembrolizumab arm. The proportion of the patients in the DM health state in each arm was uncertain, since it was based on immature RFS data and the model is sensitive to the parametric functions chosen for extrapolation; and

- The ESC noted that █% of adjuvant pembrolizumab patients who experienced a distant metastasis at least 18 months from baseline were retreated with pembrolizumab; the remaining █% received ipilimumab. The weighted cost was \$█. For those who did not receive adjuvant pembrolizumab, the model assumed █% received pembrolizumab, █% received DAB+TRAM, █% ipilimumab and █% nivolumab. The weighted cost for these patients was \$█.

6.48 The key drivers of the model are summarised below.

**Table 10: Key drivers of the model**

Description	Method/Value	Impact
RFS estimate	Parametric functions were fitted to the observed immature RFS data to select the models for RFS estimates	High, favours pembrolizumab
Costs of subsequent first-line treatments for disease recurrence	Duration of the first-line treatment was based on KN006 trial and a network meta-analysis. The ESC noted time on treatment was linked to PFS, which was likely to overestimate treatment costs and hence, cost offsets given the higher proportion of observation patients experiencing DM. The proportion of patients receiving a first-line treatment was based on the modelled proportion of patients entering DM, which was derived from the modelled RFS	High, favours pembrolizumab
Transitions from DM to death	DM to death was based on KN006 trial for those who received pembrolizumab in the advanced setting and a network meta-analysis of trials of other first-line treatments for patients who receive anti-cancer treatments other than pembrolizumab. Exponential models of OS and PFS were used for extrapolation. No other parametric functions were considered. The ESC noted that the potential effects of adjuvant pembrolizumab on the effectiveness of therapies received following DM were unknown.	High, direction is unclear.

DM = distant metastases; ESC = Economic Sub-Committee; OS = overall survival; PFS = progression free survival; RFS = recurrence-free survival

Source: Compiled during the evaluation based on Section 3 of the submission.

6.49 The results of the modelled economic evaluation are summarised below. The PSCR provided an updated model incorporating updated estimated SPA discounts for PBS listed treatment in the advanced setting. It was unclear how the PSCR estimated the SPA discounts. The effect on the ICER was minimal.

Table 11: Results of the economic evaluation

Component		Pembrolizumab	Observation	Increment
Costs	Adjuvant therapy	\$ [redacted]	\$ [redacted]	\$ [redacted]
	Subsequent therapies	\$ [redacted]	\$ [redacted]	-\$ [redacted]
	Managing AEs	\$ [redacted]	\$ [redacted]	\$ [redacted]
	Disease management	\$ [redacted]	\$ [redacted]	-\$ [redacted]
	Terminal care	\$ [redacted]	\$ [redacted]	-\$ [redacted]
	<b>Total</b>	<b>\$ [redacted]</b> <b>PSCR: \$ [redacted]</b>	<b>\$ [redacted]</b> <b>PSCR: \$ [redacted]</b>	<b>\$ [redacted]</b> <b>PSCR: \$ [redacted]</b>
QALYs	Recurrence-free	[redacted]	[redacted]	[redacted]
	Locoregional recurrence	[redacted]	[redacted]	[redacted]
	Distant metastases	[redacted]	[redacted]	[redacted]
	<b>Total</b>	[redacted]	[redacted]	[redacted]
LYG	Recurrence-free	[redacted]	[redacted]	[redacted]
	Locoregional recurrence	[redacted]	[redacted]	[redacted]
	Distant metastases	[redacted]	[redacted]	[redacted]
	<b>Total</b>	[redacted]	[redacted]	[redacted]
<b>Incremental cost/extra QALY</b>				<b>\$ [redacted]</b> <b>PSCR: \$ [redacted]</b>
<b>Incremental cost/extra LYG</b>				<b>\$ [redacted]</b>

AE = adverse event; AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity; LYG = life year gained; PFS = progression free survival; PSCR = Pre-Sub-Committee Response; QALY = quality-adjusted life year; SPA = Special Pricing Arrangement.

Source: Tables 3-23 and 3-24, Section 3 of the submission and Amended base case provided in the PSCR.

PSCR changes: application of estimated SPA discounts applied to the AEMP instead of the DPMQ, adding the distinct option for treatment with vemurafenib+cobimetinib in the advanced setting, provision of additional specificity in the value for estimated PFS from KN006, and fees and mark-ups updated to be effective 1 July 2018.

The redacted table shows ICERs in the range of \$15,000 - \$45,000 per QALY or LY gained.

- 6.50 The incremental cost-effectiveness ratio (ICER) stabilised at approximately 10 years (the time horizon in the submission’s base case).
- 6.51 The submission presented a range of univariate sensitivity analyses. As noted earlier, the model is sensitive to the distribution models used to estimate the treatment effect. The other key uncertainties associated with the treatment effect of first-line therapies in advanced setting could be not addressed in sensitivity analyses.
- 6.52 The PSCR provided a number of sensitivity analyses to test the impact of the theory that patients who received adjuvant pembrolizumab respond differently to treatment in the advanced setting (see Table 12). The PSCR claimed that the relative effectiveness of treatment in the advanced setting was not a significant driver of the model. The ESC considered the small changes in the ICER were due to both the costs and benefits being adjusted.
- 6.53 A number of additional sensitivity analyses suggested by ESC are also presented.

Table 12: Sensitivity analyses

Scenario	ICER
1 Base case	\$ [REDACTED]
<b>Effectiveness of treatment in the advanced setting – presented in the PSCR</b>	
2 20% reduction in the effectiveness* of pembrolizumab in the advanced setting for patients who had received adjuvant pembrolizumab and were eligible for re-challenge under the proposed listing	\$ [REDACTED]
3 Scenario 2 AND 20% reduction in the effectiveness* of all treatments in the advanced setting for patients who had received adjuvant pembrolizumab and were not eligible for re-challenge under the proposed listing.	\$ [REDACTED]
4 20% increase in the effectiveness* of all treatments in the advanced setting for patients in the observation strategy, on the basis that the exponential survival curves applied in the model already likely underestimate the treatment benefit.	\$ [REDACTED]
5 No option for re-challenge with pembrolizumab	\$ [REDACTED]
<b>Additional sensitivity analyses – suggested by ESC</b>	
6 Using the exponential parametric functions to determine the transition probabilities for the RF → LR and RF → DM health states	\$ [REDACTED]
7 Not allowing rechallenge with pembrolizumab following adjuvant pembrolizumab among eligible patients	\$ [REDACTED]
8 Utility values from KN-006 as reported in the March 2016 Pembrolizumab commentary (DM pre-progression = [REDACTED]; DM post-progression = [REDACTED])	\$ [REDACTED]
9 Reducing the cost of subsequent therapies by 20% (as a proxy for reducing ToT)	\$ [REDACTED]
10 #6 and #7 and #8 and #9	\$ [REDACTED]

DM = distant metastases; ICER = incremental cost-effectiveness ratio; LR = locoregional; OS = overall survival; PFS = progression free survival; PSCR = pre-Sub-Committee response; RF = recurrence free; ToT = time on treatment

Source: Table 1, p6 of the PSCR

\* Expected PFS weeks and OS weeks

The redacted table shows ICERs in the range of \$15,000/QALY - \$45,000/QALY and \$45,000/QALY - \$75,000/QALY.

6.54 The pre-PBAC Response stated that the use of the exponential parametric functions (#6 above) provided the least best fit and was misaligned with the natural history data for placebo. The PBAC agreed that use of the exponential parametric function resulted in an inappropriate function, noting that the ESC was trying to assess the extent of modelled benefit of PD-1 inhibitor treatment in both the adjuvant and unresectable settings as the costs and effectiveness of treatments in the post-progression setting were based on external data.

**Drug cost/patient/course: \$ [REDACTED]**

6.55 The cost of treatment with pembrolizumab for the average patient is \$ [REDACTED] based on an ex-manufacturer price of \$ [REDACTED]/100mg vial, 200 mg fixed dosing at every three weeks for one year, and an average of [REDACTED] administrations per patient and a private: public split of 68.5%:31.5%. The submission also estimated an average of \$ [REDACTED] in drug administration costs. This figure differed from that used in the financial estimates, which contained a referencing error, and different assumptions regarding private vs public hospital split, and application of the \$20 TGA licensed compounders' fee.

**Estimated PBS usage & financial implications**

6.56 This submission was not considered by DUSC.

- 6.57 The spreadsheet detailing the financial estimates contained a number of errors.
- 6.58 The submission used an epidemiological approach to estimate the use and financial impact of the proposed medicine. The number of patients expected to be treated with pembrolizumab in the adjuvant setting was based on:
- The incident population newly diagnosed with Stage III disease, estimated from a linear extrapolation of incident data from 2007 to 2014 (AIHW melanoma of the skin book) and estimated incidence rates from 2016 (Skin Cancer in Australia) and 2017 (Cancer in Australia 2017), multiplied by the proportion of annual incidence (new cases) that is Stage III (8%). This was based on a 2002 publication utilising data from the Sydney Melanoma Institute<sup>+++</sup>. Although this data source is older, this value is consistent with data from the NSW Central Cancer registry which estimated at the time of diagnosis, 8.5% had Stage III disease (NSW Cancer Institute NSW 2010).
  - Incident patients initially diagnosed with earlier stages of disease that progress to Stage III. The submission assumed that 55% of patients with Stage III disease were initially diagnosed with earlier stages of disease, based on data from the Melanoma Institute of Australia<sup>+++</sup>. This data source appeared reasonable.
  - The proportion of prevalent patients diagnosed in the three months prior to listing that would also be eligible for treatment with pembrolizumab (i.e. likely have undergone surgical resection within the previous three months);
  - The submission assumed that 89% of Stage III cases were resectable<sup>§§§</sup>. This figure could not be verified from the cited paper. The PSCR clarified that the SEER data indicated that 11% of patients with Stage III disease did not have surgery (i.e. unresected disease); therefore, 89% of patients were resected.

---

<sup>+++</sup> Kefford R. Adjuvant therapy of cutaneous melanoma: the interferon debate. *Annals of Oncology*. 2003; 14(3): 358-365.

<sup>+++</sup> Haydu L, Scolyer R, Lo S, et al. Conditional survival: an assessment of the prognosis of patients at time points after initial diagnosis and treatment of locoregional melanoma metastasis. *Journal of Clinical Oncology*. 2017; 35(15): 1721.

<sup>§§§</sup> Kosary C, Altekruze S, Ruhl J, et al. Clinical and prognostic factors for melanoma of the skin using SEER registries: Collaborative Stage Data Collection System, Version 1 and Version 2. *Cancer*. 2014; 120(23): 3807-3814.

- 6.59 The submission assumed an expected uptake rate of ■%. The PBAC considered that this uptake rate was high as older patients are more likely to be observed than undergo surgical resection and those with earlier stages of disease (i.e. Stage IIIA and IIIB using the 8<sup>th</sup> edition of the AJCC melanoma staging manual) may be less likely to receive treatment. The PSCR considered that a high rate of uptake would be expected, stating that the Australian Institute of Health and Welfare reported that approximately 8% of patients were over the age of 85 at diagnosis. The PSCR also cited Haydu 2017, a recent Australian study of over 4,000 Stage III patients, which reported that patients with Stage III melanoma (adjusted to the 8<sup>th</sup> edition AJCC melanoma staging system) were relatively young (median age of 59 years) and that approximately 4.8% of patients were diagnosed with Stage IIIA disease. The PBAC noted that Haydu 2017 reported that 44.2% of patients had Stage IIIB at diagnosis, 37.6% Stage IIIC and 2.3% Stage IIID. Overall, the PBAC considered the number of patients to be treated with pembrolizumab to be overestimated.
- 6.60 Although the submission stated that a number of cost-offsets (associated with avoidance of recurrence), and additional costs to other health budgets (e.g. administration costs) were likely to occur, the submission did not include these in their financial estimates. The PSCR stated that these offsets were not included as the offsets would not be materialised, based on the current melanoma risk-share arrangement. The PBAC noted that cost-offsets for post-progression treatment were applied in the model.

Public Summary Document – November 2018 PBAC Meeting

Table 13: Estimated use and financial implications

		Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
A	Total patients treated (█% uptake rate)	█	█	█	█	█	█
B	Number of administrations of adjuvant pembrolizumab (█ per patient)	█	█	█	█	█	█
C	Average cost per administration (AEMP)	\$█					
<b>Total cost by scheme (PBS/RPBS) (\$)</b>							
D	PBS (BxCx98.4%)	█	█	█	█	█	█
	Revised (BxCx95%)	█	█	█	█	█	█
E	RPBS (BxCx1.6%)	█	█	█	█	█	█
	Revised (BxCx5%)	█	█	█	█	█	█
F	Total cost of pembrolizumab (BxC=D+E)	█	█	█	█	█	█
	Revised	█	█	█	█	█	█
<b>Less copayments (\$)</b>							
G	Number of co-payments per patient by treatment year	2					
	Revised	3					
H	Average co-payment	█					
I	PBS	█	█	█	█	█	█
	Revised	█	█	█	█	█	█
J	RPBS	█	█	█	█	█	█
	Revised	█	█	█	█	█	█
K	Total co-payments	█	█	█	█	█	█
	Revised	█	█	█	█	█	█
<b>Net cost of adjuvant pembrolizumab to the PBS/RPBS (\$)</b>							
L	PBS (D-I)	█	█	█	█	█	█
	Revised	█	█	█	█	█	█
M	RPBS (E-J)	█	█	█	█	█	█
	Revised	█	█	█	█	█	█
N	Total (F-K=L+M)	█	█	█	█	█	█
	Revised	█	█	█	█	█	█

AEMP = approved ex-manufacturer price; PBS = Pharmaceutical Benefits Schedule; RPBS = Repatriation Pharmaceutical Benefits Schedule

Source: Table 4.2-6, Table 4.3-4, and Table 4.3-5 Section 4

Revised: Corrected referencing error for the Public versus Private hospital usage split (these values were reversed), and updated to reflect three patient co-payments (from two) per patient per course, consistent with the requested listing.

*The redacted table shows that at Year 6 the estimated number of patients was less than 10,000 per year, and the net cost to the PBS would be more than \$100 million per year.*

### **Quality Use of Medicines**

- 6.61 The submission outlined a number of activities to promote the safe and effective use in clinical practice, including the development of educational materials, and the delivery of education programs.

### **Financial Management – Risk Sharing Arrangements**

- 6.62 The sponsor indicated that they were willing to enter into a RSA, that would include a SPA as well as annual subsidisations caps based on appropriate patient numbers.
- 6.63 The submissions stated that in order to structure reasonable RSAs that accommodate adjuvant treatment for resected Stage III patients, it is important to also take into account the existing deed for unresectable Stage III and Stage IV advanced melanoma patients due to the interdependence between the two populations. The ESC noted that the market size for unresectable melanoma could potentially change if pembrolizumab was PBS-subsidised for adjuvant therapy.
- 6.64 If pembrolizumab were to be listed in the Stage III adjuvant setting, then the sponsor would be willing to negotiate a RSA that allows for the treatment of melanoma patients across the adjuvant and metastatic settings based on appropriate patient numbers and a rebate that is a proportion of costs above the subsidisation caps. For example, a structure and rebate that mirrors [REDACTED]
- 6.65 In the PSCR and pre-PBAC Response, the sponsor stated that they would welcome feedback on whether a Managed Entry Scheme could help address any uncertainty surrounding overall survival outcomes of pembrolizumab treatment in the adjuvant setting versus in the advanced setting.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend listing of pembrolizumab as an adjuvant treatment for completely resected Stage III melanoma. The PBAC acknowledged that there was a high unmet clinical need for effective therapies to reduce the risk of recurrence of resected Stage III melanoma, and considered that in some circumstances recurrence was less likely for those treated with pembrolizumab compared to placebo. However, the PBAC noted the prognosis for Stage III patients varied widely depending on staging subgroup and considered the appropriate population for treatment had not been identified in the submission. The PBAC considered that there was uncertainty in the magnitude of the clinical benefit given the limited duration of follow-up in the trial and this resulted in a highly uncertain incremental cost-effectiveness ratio (ICER). In addition, the estimated financial impact was very high and uncertain.
- 7.2 The PBAC acknowledged the consumer comments, which were supportive of listing

- pembrolizumab for the treatment of completely resected Stage III melanoma. The PBAC also noted the strong support from the Medical Oncology Group of Australia.
- 7.3 The PBAC considered that the nominated comparator, observation, was reasonable in this submission.
- 7.4 The PBAC noted that the submission had considered the place in therapy for pembrolizumab in both the resected and unresected melanoma populations. In addition to providing proposed PBS restrictions for patients with completely resected Stage III disease, the submission provided a proposed restriction for retreatment with pembrolizumab in the unresectable setting. The PBAC was concerned by the complete lack of comparative evidence for, and the potential unknown downstream consequences of, retreatment with programmed cell death-1 (PD-1) inhibitor therapies in terms of efficacy, safety and cost-effectiveness. If pembrolizumab becomes available for use as an adjuvant therapy, it will alter the use of PD-1 inhibitors in the unresectable setting and this impact, particularly in terms of overall survival, remains an area of uncertainty.
- 7.5 In terms of adjuvant pembrolizumab use, the submission was based on one randomised controlled trial, KN054, which compared pembrolizumab with placebo in patients with Stage III resectable melanoma. The submission proposed that pembrolizumab be used in all patients with Stage III resectable disease.
- 7.6 Trial KN054 classified melanoma stage using the 7<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) melanoma staging system, which has three Stage III subgroups (IIIA, IIIB and IIIC). The PBAC noted that KN054 recruited patients with predominantly Stage IIIB (46% of patients) and Stage IIIC (38% of patients) disease. Patients with Stage IIIA (which represented 16% of the trial population) were recruited only if they had metastases greater than 1 mm. Therefore, patients with disease that was less advanced (Stage IIIA with metastases < 1 mm) were not represented in the trial population.
- 7.7 Patients are now classified (from 2018) using the 8<sup>th</sup> edition of the AJCC melanoma staging system, which has four subgroups (IIIA, IIIB, IIIC and IIID). The PBAC noted that five- and ten-year survival rates were quite different between the 7<sup>th</sup> and 8<sup>th</sup> edition sub-stages – five-year survival rates for Stages IIIA, IIIB and IIIC using the 7<sup>th</sup> edition were estimated to be 78%, 59% and 40% respectively; whereas, using the 8<sup>th</sup> edition, five-year melanoma specific survival probabilities for Stages IIIA, IIIB, IIIC and IIID were 93%, 83%, 69% and 32% (see Figure 1). The PBAC noted the limitations associated with comparing different patient cohorts; however, considered that patients in the 8<sup>th</sup> edition cohort had a more favourable survival profile across Stages IIIA, IIIB, and IIIC disease compared with patients with similar stage groupings in the 7<sup>th</sup> edition. The PBAC considered that by recruiting patients with Stage IIIA (metastasis > 1 mm), Stage IIIB and IIIC disease (using the 7<sup>th</sup> edition) the trial population had disease with a poorer prognosis compared with the proposed PBS population (all Stage III patients using the 8<sup>th</sup> edition). The PBAC noted the submission had not addressed the

implications of this difference on the likely cost-effectiveness of pembrolizumab for adjuvant treatment. Given this, the PBAC considered the appropriate patient population for treatment with adjuvant pembrolizumab remained unclear.

- 7.8 The primary outcome of KN054 was recurrence free survival (RFS). The PBAC noted that the data were immature and, that at the median duration of follow-up (16 months), the median RFS for pembrolizumab had not been reached. The hazard ratio was 0.57 (95% confidence interval: 0.43, 0.74). The PBAC considered that the submission's claim that pembrolizumab was superior to placebo in terms of RFS, based on the interim analysis of KN054, was reasonable for the trial population. However, due to the immaturity of the trial data, the PBAC considered that the magnitude of the treatment effect was highly uncertain and the impact on overall survival was unknown. The PBAC considered the magnitude of RFS benefit for patients with Stage IIIA (metastases > 1 mm) was highly uncertain due to the small proportion of patients with this sub-stage of disease recruited into the trial.
- 7.9 The PBAC noted that the submission did not make a claim regarding the safety of pembrolizumab. The PBAC considered that pembrolizumab was inferior to placebo in terms of safety in the treatment of resectable Stage III melanoma.
- 7.10 The PBAC considered that the ICER presented in the submission was highly uncertain, variable and likely underestimated. The PBAC raised a number of concerns, including:
- that the model population, which was informed by the trial population, had a poorer prognosis than the likely PBS population;
  - that overall survival in both the pembrolizumab (■■■■% at five years and ■■■■% at 10 years) and placebo (■■■■% at five years and ■■■■% at 10 years) arms of the model was low when compared to melanoma specific survival probabilities presented in the 8<sup>th</sup> edition of the AJCC Staging Manual, which estimated five- and 10-year rates of 77% and 69% respectively for Stage III patients;
  - that the modelled data were based on immature RFS trial evidence (median RFS for pembrolizumab had not yet been reached) and that no overall survival data were available;
  - that the quantification of the relationship between RFS and overall survival was uncertain, and the impact of treatment for recurrence on this relationship unknown; and
  - the relevance of post-recurrence inputs for the adjuvant pembrolizumab arm, given that there was no efficacy or safety data for patients who received a PD-1 inhibitor in both the adjuvant and unresectable settings. In addition, the cost and effectiveness of treatments post-progression were based on progression free survival and overall survival curves derived from external evidence (KN006 and a network meta-analysis). Use of these data in the model introduced substantial uncertainty which could not be addressed by the sensitivity analyses.

- 7.11 Although the PBAC considered that utilisation estimates were overestimated, the financial impact was also very high (more than \$100 million per year for less than 10,000 patients). The PBAC noted that cost-offsets for post-progression treatment were applied in the economic model, but not similarly applied in the financial estimates.
- 7.12 The PBAC considered that the average number of administrations per patient (██████ per year) overestimated the dose intensity and the cost per patient as █████% of patients in KN054 did not complete one year of treatment. In addition, the PBAC considered that the rate of uptake, █████%, applied in the submission was high as:
- older patients, particularly those with comorbidities, autoimmune conditions and/or poor performance status, may be less likely to receive adjuvant therapies; and
  - those with earlier stage disease (i.e. Stages IIIA and IIIB using the 8<sup>th</sup> edition of the AJCC melanoma staging system) may be less likely to receive adjuvant pembrolizumab treatment. Noting that in Australia, 49% of Stage III melanoma patients are diagnosed at Stage IIIA or IIIB (8<sup>th</sup> edition), the PBAC considered that a review of the uptake rates across the Stage III subgroups was warranted.
- 7.13 The PBAC considered that a Managed Entry Scheme might help address some of the uncertainty surrounding the use of pembrolizumab in the adjuvant setting in terms of the incremental benefit, including overall survival in patients with more advanced Stage III disease.
- 7.14 The PBAC considered that any future resubmission should be a major resubmission which:
- considers the risk benefit ratio and cost-effectiveness of pembrolizumab across the Stage III subgroups;
  - addresses the issues noted by the ESC and the PBAC regarding the economic model and the financial impact estimations; and
  - if available, provides data with additional follow-up for the KN045 trial.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

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

## **9 Sponsor's Comment**

The sponsor had no comment.