

## 5.19 PEMBROLIZUMAB

50 mg vial, 100 mg vial;

Keytruda®; Merck Sharpe & Dohme (Australia) Pty Ltd

### 1 Purpose of Application

- 1.1 Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required listing for the treatment of unresectable Stage III or Stage IV metastatic melanoma.

### 2 Requested listing

- 2.1 The requested restriction is provided below, including initial and continuing treatment criteria as well as the proposed grandfathering provision. Suggestions and additions proposed by the Secretariat and by the ESC to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB				
50 mg injection: powder for, 1 vial	<del>280mg</del>	5	\$ [REDACTED] (Public)	Keytruda MK
100mg injection: powder for, 1 vial	240 mg		\$ [REDACTED] (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>Episodicity:</b>	-
<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 Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	-

Public Summary Document – March 2015 PBAC Meeting

<b>Clinical criteria:</b>	The treatment must be the sole PBS-subsidised therapy for this condition;  AND  Patient must be negative for a BRAF V600 mutation;  AND  <i>The condition must be previously untreated;</i>  AND  <i>The treatment must not exceed a total of 6 doses at a maximum dose of 2mg/kg every 3 weeks.</i>
<b>Population criteria:</b>	-
<b>Foreword</b>	-
<b>Definitions</b>	-
<b>Prescriber Instructions</b>	<i>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.</i>
<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.  <i>No increase in the maximum number of repeats may be authorised.</i>
<b>Cautions</b>	-

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB				
50 mg injection: powder for, 1 vial	280mg	5	\$ [REDACTED] (Public)	Keytruda MK
100mg injection: powder for, 1 vial	240 mg		\$ [REDACTED] (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>Episodicity:</b>	-
<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 treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

Public Summary Document – March 2015 PBAC Meeting

<b>Treatment criteria:</b>	-
<b>Clinical criteria:</b>	<p>The treatment must be the sole PBS-subsidised therapy for this condition;</p> <p>AND</p> <p>Patient must be positive for a BRAF V600 mutation;</p> <p>AND</p> <p><del>Patient</del> <i>The condition must have progressed following treatment with a BRAF inhibitor or treatment with a BRAF inhibitor is contraindicated or not tolerated unless contraindicated or not tolerated according to the TGA approved Product Information;</i></p> <p>AND</p> <p><i>The condition must be previously untreated with ipilimumab;</i></p> <p>AND</p> <p><i>The treatment must not exceed a total of 6 doses at a maximum dose of 2 mg/kg every 3 weeks.</i></p>
<b>Population criteria:</b>	-
<b>Foreword</b>	-
<b>Definitions</b>	-
<b>Prescriber Instructions</b>	<i>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.</i>
<b>Administrative Advice</b>	<p>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.</p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p>
<b>Cautions</b>	-

Public Summary Document – March 2015 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB				
50 mg injection: powder for, 1 vial	280mg	7	\$ [REDACTED] (Public)	Keytruda MK
100mg injection: powder for, 1 vial	240 mg		\$ [REDACTED] (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>Episodicity:</b>	-
<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>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	-
<b>Clinical criteria:</b>	The treatment must be the sole PBS-subsidised therapy for this condition;  AND  Patient must have previously been issued with an authority prescription for this drug <i>for this condition</i> ;  AND  Patient must have stable or responding disease;  AND  <i>The treatment must not exceed a maximum dose of 2 mg/kg every 3 weeks.</i>
<b>Population criteria:</b>	-
<b>Foreword</b>	-
<b>Definitions</b>	-
<b>Prescriber Instructions</b>	-
<b>Administrative Advice</b>	<i>No increase in the maximum number of repeats may be authorised.</i>
<b>Cautions</b>	-

Public Summary Document – March 2015 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB				
50 mg injection: powder for, 1 vial	280mg	5	\$ [REDACTED] (Public)	Keytruda MK
100mg injection: powder for, 1 vial	240 mg		\$ [REDACTED] (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>Episodicity:</b>	-
<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>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	-
<b>Clinical criteria:</b>	<del>Continuing PBS subsidised treatment of a patient who is receiving treatment with pembrolizumab at the time of application and has stable or responding disease</del>  <i>The treatment must be the sole PBS-subsidised therapy for this condition;</i>  AND  <i>The treatment must be for continuing therapy in a patient who commenced treatment with pembrolizumab prior to [listing date];</i>  AND  <i>Patient must have stable or responding disease;</i>  AND  <i>The treatment must not exceed a maximum dose of 2 mg/kg every 3 weeks.</i>
<b>Population criteria:</b>	-
<b>Foreword</b>	-
<b>Definitions</b>	-
<b>Prescriber Instructions</b>	-
<b>Administrative Advice</b>	<i>No increase in the maximum number of repeats may be authorised.</i>
<b>Cautions</b>	-

- 2.2 The submission sought listing in the context of a managed entry scheme (MES) on the basis of a cost-utility analysis compared to ipilimumab.
- 2.3 The Pre-Sub-Committee Response (PSCR, p3) proposed that the restriction wording for BRAF wild-type patients be updated to state “The condition must be previously untreated with immunotherapy agents.” As the intended interpretation was to limit use to ipilimumab-naïve patients, it was not clear why this proposal should not also apply to BRAF mutant patients.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### **3 Background**

- 3.1 TGA status: a positive TGA Delegate’s Overview was provided on 19 February 2015, after the ESC meeting. Pembrolizumab was scheduled to be discussed by the ACPM on 10 April 2015.
- 3.2 Pembrolizumab was submitted to the TGA on 6 August 2014 and there was no TGA documentation available at the time of evaluation. The submission indicated that the TGA had agreed to accelerate the assessment of pembrolizumab.
- 3.3 The submission requested listing for both the 50 mg lyophilized powder for solution and the 100 mg vial of solution for infusion forms, although the 100 mg solution for infusion is not included in the regulatory submission being considered by the TGA. The 100 mg vial has therefore been removed from the PBAC-recommended restriction.
- 3.4 The submission stated in its Subsection B.2.3 (p84) that the main indication being sought was for first-line ipilimumab-naïve patients. However, the proposed TGA indication does not specify line of use or restrict prior use of ipilimumab.
- 3.5 This was the first consideration of pembrolizumab by the PBAC. The PBAC has recently considered ipilimumab (November 2012), vemurafenib (March 2013), dabrafenib (July 2014) and trametinib (November 2014) for the treatment of unresectable Stage III or Stage IV metastatic melanoma.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

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

- 4.1 The submission reported that unresectable stage III or metastatic stage IV melanoma has a poor prognosis, with median survival of 6 to 9 months and a three-year survival rate of 10% to 15%. This is a survival rate for patients with advanced melanoma with dissemination to distant sites and visceral organs. Survival rates based on the American Joint Committee on Cancer (AJCC) Melanoma Staging Database range from 24% to 68% for 10 year survival for stage III and 10% to 15% for stage IV. These estimated survival rates pre-date the PBS listing of ipilimumab and dabrafenib and consequently may not reflect current prognosis.

- 4.2 For patients who test negative for a BRAF mutation (BRAF wild type), treatment with ipilimumab is received as first-line therapy. For patients who test positive for a BRAF mutation, treatment with a BRAF inhibitor is received as first-line therapy. The submission proposed that PBS listing of pembrolizumab would displace ipilimumab into second-line therapy for BRAF wild-type patients and into third-line therapy for patients with BRAF mutations. The ESC considered that the likely treatment algorithm has yet to be established with the addition of pembrolizumab, and is likely to be influenced also by whether therapies acting via the immune system displace BRAF inhibitors as first-line therapy in patients with BRAF mutations.

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

## **5 Comparator**

- 5.1 Ipilimumab. While this is the appropriate comparator given current treatment practice, there are ongoing trials assessing the combination of pembrolizumab and ipilimumab as well as the combination of pembrolizumab, dabrafenib and trametinib. This suggests that future treatment patterns may change.
- 5.2 The submission used a comparison with nivolumab, another PD-1 inhibitor, in its Subsection C.8 to assess its extrapolation of data for the modelled evaluation. Given the similarity in class of drug, it is likely that nivolumab may be a relevant comparator in the near future.

*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 sponsor clarified the patient population that would be covered by the requested restriction, namely, ipilimumab-naïve patients, stating that the sponsor would provide compassionate access to pembrolizumab for any patient refractory to ipilimumab. The sponsor did not specify how long this compassionate access program would last, but suggested it may be around 2 years. The sponsor also made it clear that pembrolizumab should be used following the BRAF/MEK inhibitors in patients with BRAF-mutant tumours until current clinical trials were completed.
- 6.2 The sponsor also sought to clarify the dose of pembrolizumab, stating that 2 mg/kg every three weeks appears to be equivalent to 10 mg/kg every two or three weeks. The PBAC considered that the hearing was not particularly informative as it did not add substantively to the evidence presented in the submission. The hearing did however provide reassurance that the sponsor would make pembrolizumab available to ipilimumab-refractory patients under a compassionate access program.

### **Consumer comments**

- 6.3 The PBAC noted and welcomed the input from individuals (275), health care professionals (7) and organisations (5) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pembrolizumab including outstanding benefits in overall survival with very few side effects, with consumers considering pembrolizumab to be far superior to treatment with ipilimumab.
- 6.4 A consumer hearing was held between the Australian Melanoma Consumer Alliance, Melanoma Patients Australia, CanSpeak Australia and representatives of the PBAC. The hearing highlighted that patients have a high level of belief in the effectiveness of pembrolizumab, and are extremely eager for early access to the drug. The representatives informed PBAC that there is a perception that up to 90% of patients could expect to respond to pembrolizumab, even if this is not reflected in the data presented by the sponsor to the PBAC. Consumers also believed that the response to pembrolizumab is “durable and sustained”. The PBAC was concerned at the mismatch between the public expectations of the drug and the data submitted in support of its subsidy application.
- 6.5 It was also noted that patients believe that the risks associated with early access to this drug were accepted by many, because of the perception of gaining a life-saving response.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### **Chronology of submission**

- 6.6 The PBAC noted that, following lodgement of the submission on 5 November 2014, an extraordinary amount of important additional information was provided throughout the process of evaluation, as follows:
- 24 November 2014: trial data from KN-002 provided by the sponsor (20 slides)
  - 28 January 2015: revised model and revised managed entry scheme (MES) proposal with the PSCR (16 pages)
  - 13 February 2015 (after the ESC meeting): early results of KN-006 provided by the sponsor (38 pages)
  - 17 February 2015: TGA delegate’s overview provided by the sponsor (96 pages)
  - 25 February 2015: Attachment and PES Addendum to the ESC Advice to comment on the additional post-submission information (20 pages)
  - 4 March 2015: further sensitivity analyses for the revised model and suggestions for the MES proposal with the pre-PBAC response (24 pages)
  - 6 March 2015: additional information provided by the sponsor on proposed subsidised access to pembrolizumab for ipilimumab-refractory patients via a funding arrangement from the sponsor (2 pages).
- This was in addition to five meetings with the Department before the submission was lodged (3 December 2013, 13 May 2014, 27 August 2014, 28 August 2014, and 5 September 2014) and two post-submission meetings (10 December 2014 and 2 March 2015) between the sponsor and the Department.

- 6.7 The PBAC appreciated that randomised trial data directly comparing pembrolizumab with ipilimumab in ipilimumab-naïve patients (KN-006) was eventually revealed late in the process. However, the Committee considered that the volume and timing of provision of information was counterproductive as the new data could not be extensively evaluated nor was it translated into an appropriate modelled economic evaluation. The provision of extraordinarily large post-submission documents had placed an unreasonable pressure on the PBAC's supporting processes, and evaluation capacity, particularly just prior to the PBAC meeting. As a consequence, there was insufficient time to comprehensively evaluate all the material provided, and address relevant matters such as the open-label design, the potential for differences in drop-out rates between the trial arms, and the difference between the pembrolizumab dosage regimens in KN-006 and the dosage regimen requested for TGA approval and PBS subsidy. Also, since much of the material relating to KN-006 was accepted as being provided on a confidential basis, it would be redacted from the published version of the PBAC Outcomes document and of the Public Summary Document, unless permission is granted by the sponsor or it is published elsewhere between the time of the PBAC meeting and these PBAC-derived publications.

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

### **Clinical comparisons**

#### **Original submission (5 November 2014)**

#### **Clinical trials**

- 6.8 The original submission was based on selected subgroups from an uncontrolled, non-comparative phase 1 multi-cohort pembrolizumab trial (KN-001) and a single arm from a randomised, double blind trial of ipilimumab (Hodi 2010). This clinical comparison remained the basis for the different versions of the modelled economic evaluation provided for PBAC consideration.
- 6.9 Details of the trials presented in the submission are provided in the table below.

**Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Selected trials</b>		
KN-001	Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non- Small Cell Lung Carcinoma.  Part B1: Hamid O, Robert C, Daud A, Hodi FS et al. Safety and Tumour Responses with Lambrolizumab (Anti-PD-1) in Melanoma.  Part B2: Robert C, Ribas A, Wolchok JD, Hodi FS et al. Anti-programmed-death- receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial.	May 2014  <i>NEJM</i> 2013; 369: 134-44  <i>Lancet</i> 2014; 384: 1109-17
Hodi 2010	F.S Hodi, S.J. O'Day, D.F. McDermott, R.W. Weber et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma.	<i>NEJM</i> 2010; 363(8):711-723

Source: Table B.2-1, p82-84 of the submission

6.10 Trial KN-001 is an uncontrolled, phase 1, multi-cohort trial assessing the safety, tolerability, pharmacokinetics, pharmacodynamics and anti-tumour activity of pembrolizumab in several different diseases. Pembrolizumab dosage regimens included 10 mg/kg every 2 weeks (Q2W), 10 mg/kg every 3 weeks (Q3W), and 2 mg/kg Q3W. Progression-free survival (PFS) and overall survival (OS) were included as secondary outcomes, with overall response rate being the primary outcome. The definition of events which constitute “progression” for the purposes of PFS, how these events were assessed, and by whom, were not compared across the sources of evidence for the KN-001 comparison with Hodi 2010, and so it could not be confidently concluded that this outcome is the same across these sources.

6.11 The key features of the KN-001 and Hodi 2010 trials are summarised in the table below.

**Summary of trials used in the clinical evaluation**

Trial ID	N	Treatment arms <sup>a</sup>	Trial design	Primary outcome	Use in the economic evaluation
<b>Pembrolizumab trial</b>					
KN-001	659 <sup>b</sup>	Part B1 2 mg/kg Q3W n=22 10 mg/kg Q3W n=24 10 mg/kg Q2W n=41 Part B3 10 mg/kg Q3W n=65 10 mg/kg Q2W n=58 Part D 2 mg/kg Q3W n=51 10 mg/kg Q3W n=52	Phase I OL, MC	Overall response rate	Extrapolated PFS and OS data
<b>Ipilimumab trial</b>					
Hodi 2010 (CT-020)	676	IPI 3 mg/kg Q3W n=137	Phase II/III R, DB, MC	Overall survival	Extrapolated PFS and OS data (digitised plots of Kaplan-Meier figures)

<sup>a</sup> Only the patient sub-groups selected by the submission are included.

<sup>b</sup> The N of 659 is based on the melanoma cohorts B1, B2, B3 and D of KN-001

DB=double blind; IPI=ipilimumab; MC=multicentre; OL=open label; OS=overall survival; PFS=progression-free survival; Q2W=every 2 weeks; Q3W=every 3 weeks; R=randomised

Source: Table B.2-3, p87-88 of the submission

- 6.12 The submission selected differing cohorts using different pembrolizumab doses to provide data for efficacy and safety outcomes. As indicated in the table below, the submission used these cohorts in an inconsistent manner across the clinical and economic evaluations.

**Summary of KN-001 cohorts used in the clinical and economic evaluation**

Cohort	Treatment arms	Patient population (advanced melanoma)	Clinical evaluation		Economic evaluation
			Efficacy	Safety	
Part B1 (n=135)	2 mg/kg Q3W 10 mg/kg Q2W 10 mg/kg Q3W	IPI naïve	✓		✓
		IPI treated			✓
Part B2 (n=173)	2 mg/kg Q3W 10 mg/kg Q3W	IPI refractory			✓
Part B3 (n=248)	10 mg/kg Q2W 10 mg/kg Q3W	IPI naïve	✓	✓	
		IPI treated			
		IPI refractory			
Part D (n=103)	2 mg/kg Q3W 10 mg/kg Q3W	IPI naïve	✓	✓	✓

IPI=ipilimumab; Q2W=once every 2 weeks; Q3W=once every 3 weeks  
Source: p97-101 of the Clinical Study Report (CSR) for KN-001

### **Comparative effectiveness**

- 6.13 The table below provides a summary of PFS and OS data from KN-001 for pembrolizumab alongside ipilimumab data from Hodi 2010 as follows:

- as presented in the submission, based on the ipilimumab-naïve groups of KN-001 melanoma participants at the April 2014 data cut<sup>1</sup>
- as compared with the two published papers (Robert et al, 2014 and Hamid et al, 2013) of Parts B2 and B1 of KN-001, respectively. It should also be noted that:
  - Robert et al, 2014 presented data excluded by the submission for ipilimumab-refractory patients from the October 2013 data cut.
  - Hamid et al, 2013 included both ipilimumab-naïve and ipilimumab-treated patients from the March 2013 data cut.

The ESC noted that the data cut dates were earlier in the published papers than submitted for PBAC consideration, and advised a general preference for PFS and OS data to be based on longer-term follow-up. The ESC noted that, even with clearer data cut information, it was not possible to ascertain if the median duration of follow-up was similar across the KN-001 and Hodi 2010 studies.

<sup>1</sup> Definitional note: 'data cut' refers to the date of analysis of data when there is planned ongoing follow-up, with further analyses at later time points.

Summary of PFS and OS results from the submission and published papers

Submission KN-001 (ipi-naïve) April 2014 data cut	Part B3 (ipi-naïve sub-group)		Part D (ipi-naïve)		Part B1 (ipi-naïve subgroup) plus Part D <sup>a</sup>			Total N=190	Hodi 2010 IPI 3 mg/kg Q3W N=137
	10 mg/kg Q3W N=65	10 mg/kg Q2W N=58	2 mg/kg Q3W N=51	10 mg/kg Q3W N=52	2 mg/kg Q3W N=73	10 mg/kg Q3W N=76	10 mg/kg Q2W N=41		
<b>Progression-free survival (RECIST independent central review<sup>b</sup>)</b>									
Progressed	39 (60.0%)	34 (58.6%)	33 (64.7%)	37 (71.2%)	48 (65.8%)	58 (76.3%)	27 (65.9%)	133 (70.0%)	NA
Median mths (95% CI)	4.1 (2.8, 8.3)	3.1 (2.8, -)	5.5 (2.8, 14.0)	4.2 (2.8, 9.9)	8.2 (2.8, 14.0)	4.2 (2.8, 6.7)	8.7 (3.3, 22.1)	5.5 (3.4, 9.0)	2.86 (2.76, 3.02)
PFS rate at 6mths	45.8%	43.5%	49.5%	41.4%	51.9%	41.6%	54.6%	48.3%	57.7%
<b>Overall survival</b>									
Died	19 (29.2%)	19 (32.8%)	19 (37.3%)	23 (44.2%)	27 (37.0%)	32 (42.1%)	13 (31.7%)	72 (37.9%)	100 (73.0%)
Median mths (95% CI)	NR (-, -)	NR (10.0, -)	NR (14.0, -)	NR (9.5, -)	NR (21.1, -)	23.1 (16.5, -)	NR (24.4, -)	NR (22.8, -)	10.1 (8.0, 13.8)
Alive at 1 year	NR	NR	72.0%	63.5%	76.1%	67.9%	82.2%	74.0%	45.6%
<b>Robert 2014</b>									
Part B2 KN-001 (ipi-refrac) Oct 2013 data cut N=173	2 mg/kg Q3W N=89	10 mg/kg Q3W N=84	HR (95% CI)						
<b>Progression-free survival (RECIST independent central review)</b>									
Median mths (95% CI)	5.1 (2.8, 8.3)	3.2 (2.8, 5.5)	0.84 (0.57, 1.23)						
PFS rate at 6mths	45%	37%	-						
<b>Overall survival (May 2014)</b>									
Difference 2 mg/kg vs. 10 mg/kg			1.09 (0.68, 1.75)						
Alive at 1 year	58%	63%	-						
<b>Hamid 2013</b>									
Part B1 KN-001 (ipi-naïve and ipi- treated) Mar 2013 data cut N=135	2 mg/kg Q3W ipi-naïve N=22	10 mg/kg Q3W ipi-naïve N=24	10 mg/kg Q3W ipi-treated N=32	10 mg/kg Q2W ipi-naïve N=41	10 mg/kg Q2W ipi-treated N=16	Total N=135			
<b>Progression-free survival</b>									
Median mths	Not provided					>7 mths			

<sup>a</sup> The pooled Part B1 ipi-naïve and Part D cohorts of KN-001 provided the data used for extrapolation in the submission's modelled evaluation.

<sup>b</sup> Also identified in the submission as integrated radiology and oncology assessment (IRO).

HR=hazard ratio; ipi=ipilimumab; mths=months; OS=overall survival; PFS=progression-free survival; Q2W=every 2 weeks; Q3W=every 3 weeks; refrac=refractory

Source: Table B.6-4, p119 of the submission; KN-001 Updated Data Tables p17-22; Robert et al 2014; Hamid et al 2013.

- 6.14 There is considerable variation in outcomes across the dose groups and cohorts, with median PFS ranging from 3.1 months (10 mg/kg Q2W in Part B3) to 8.2 months in the 2 mg/kg Q3W group and 8.7 months in the 10 mg/kg Q2W group in the pooled Part B1 plus D. This range of values highlights the immaturity of the data.
- 6.15 Median OS has not yet been reached in any of the dose groups or cohorts, with the exception of the 10 mg/kg Q3W dose group in the pooled B1 plus D cohort (23.1 months; 95% CI; 16.5, -).
- 6.16 In contrast to the impression of a 90% response rate expressed by consumers, the overall response rate reported for the different subgroups of KN-001 ranged between

33% and 37%: 33% for ipilimumab-naïve patients from Part B3 (N=123); 34% for ipilimumab-naïve patients from Part D (N=103); and 37% for ipilimumab-naïve patients from Part B1 plus Part D (N=190).

### Comparative harms

- 6.17 The submission presented adverse event (AE) data only for Part B3 (ipilimumab-naïve) and Part D of trial KN-001, with AE data from the April 2014 data cut. While this data cut matches that used for the efficacy data presented, the trial cohorts differ, with no AE data provided for the pooled Part B1 (ipilimumab-naïve) plus Part D cohort, which the submission focussed on for efficacy outcomes. Another concern with the safety data presented by the submission is that the Part B3 cohort uses only the 10 mg/kg dose of pembrolizumab, but the sponsor is seeking TGA approval for only the 2 mg/kg dose. The table below provides a summary Grade 3-5 drug-related AEs as well as immune-related AEs.

Summary of adverse events in Part B3 and Part D of KN-001 and Hodi 2010

Adverse events	Part B3 ipilimumab-naïve			Part D ipilimumab-naïve			Hodi 2010 IPI N=131
	10 mg/kg Q3W N=65	10 mg/kg Q2W N=58	Total N=123	2 mg/kg Q3W N=51	10 mg/kg Q3W N=52	Total N=103	
<b>Grade 3-5 drug-related AEs</b>							
Anaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (1.0%)	4 (3.1%)
Colitis	2 (3.1%)	0 (0.0%)	2 (1.6%)	1 (2.0%)	0 (0.0%)	1 (1.0%)	7 (5.3%)
Diarrhoea	1 (1.5%)	0 (0.0%)	1 (0.8%)	1 (2.0%)	0 (0.0%)	1 (1.0%)	6 (4.6%)
Fatigue	1 (1.5%)	1 (1.7%)	3 (2.4%)	1 (2.0%)	1 (1.9%)	2 (1.9%)	9 (6.9%)
<b>Immune-related AEs</b>							
Drug-related	12 (18.5%)	8 (13.8%)	20 (16.3%)	15 (29.4%)	9 (17.3%)	24 (23.3%)	NA
Grade 3-5 drug-related	2 (3.1%)	1 (1.7%)	3 (2.4%)	2 (3.9%)	0 (0.0%)	2 (1.9%)	NA

NA=not available

Source: Table B.6-5, p123; Table B.6-6, p125 and Table B.6-7, p126-127 of the submission

- 6.18 The data presented for the submission's safety claim did not correspond to the safety data used in the model, which reflected the pooled Part B1, B2 and D cohorts.

### Benefits/harms

- 6.19 A summary of benefits and harms based on statistical comparison of pembrolizumab and ipilimumab could not be completed using the data from KN-001, given the lack of comparative data and the characteristics of the multi-cohort phase 1 pembrolizumab trial. The data presented to the PBAC for the KN-001 cohorts were compartmentalised by referring to different subgroups when reporting different outcomes. Data addressing benefits were based on the pooled Part B1 (ipilimumab-naïve sub-group) and Part D (ipilimumab-naïve) cohorts. Data addressing harms were based on the pooled Part B1 (ipilimumab-treated and ipilimumab-naïve), Part B2 (ipilimumab-refractory) and Part D (ipilimumab-naïve) cohorts. Complicating interpretation further, across the KN-001 cohorts, 3 doses of pembrolizumab were used: 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. The majority of patients were treated with a 10 mg/kg dose, which has not been submitted to the TGA for registration (62% in the pooled Part B1 and D cohort; 61% in the Parts B1, B2 and D cohort). The sponsor has not requested TGA approval for the 10 mg/kg dose of

pembrolizumab and argued in Subsection C.1 of the submission that there are no differences between the doses in outcomes (see also paragraph 6.23 below).

**Summary of benefits and harms for pembrolizumab and ipilimumab**

Trial	Pembrolizumab <sup>a</sup> N=190	Ipilimumab N=137	Absolute difference	HR (95% CI)
<b>Benefits</b>				
<b>Progression-free survival – KN-001 and Hodi 2010</b>				
PFS rate at 3 months	58.8%	57.7%	NC <sup>b</sup>	NC <sup>b</sup>
Median months (95% CI)	5.5 (3.4, 9.0)	2.86 (2.76, 3.02)	NC <sup>b</sup>	-
<b>Overall survival – KN-001 and Hodi 2010</b>				
OS rate at 12 months	74.0%	45.6%	NC <sup>b</sup>	NC <sup>b</sup>
Median months (95% CI)	NR	10.1 (8.0, 13.8)	-	-
<b>Harms</b>				
	Pembrolizumab <sup>c</sup> N=411	Ipilimumab N=131	Absolute difference	RR (95% CI)
Diarrhoea	5/411	6/131	NC <sup>b</sup>	NC <sup>b</sup>
Anaemia	14/411	4/131	NC <sup>b</sup>	NC <sup>b</sup>
Fatigue	10/411	9/131	NC <sup>b</sup>	NC <sup>b</sup>

<sup>a</sup> For PFS and OS pembrolizumab results are based on the pooled B1 (ipilimumab-naïve sub-group) and Part D (ipilimumab-naïve) cohorts; N=190 with data cut-off of April 2014. In this cohort 73 patients received 2 mg/kg Q3W, 76 received 10 mg/kg Q3W and 41 received 10 mg/kg Q2W.

<sup>b</sup> The calculation of comparative effects was not considered to be informative due to the presence of the following issues:

- Known confounders: Greater performance status of patients in the pembrolizumab trial, with proportion of patients with ECOG status of 0: KN-001 B1+D cohort 79.5%; Hodi 2010: 52.6%.
- Unknown confounders: Unquantifiable biases that exist in single arm comparisons.

<sup>c</sup> The adverse events results presented for pembrolizumab are based on those used in the modelled evaluation; the all melanoma cohort of Parts B1, B2 and D; N=411. This pooled cohort included ipilimumab-treated patients (and ipilimumab-naïve) in Part B1, ipilimumab-refractory patients in Part B2 and ipilimumab-naïve in Part D. In this cohort, 162 patients received 2 mg/kg Q3W, 192 received 10 mg/kg Q3W and 57 received 10 mg/kg Q2W.

HR=hazard ratio; NA=not available; NC=not calculated; OS=overall survival; PFS=progression-free survival; Q2W=every 2 weeks; Q3W=every 3 weeks; RR=risk ratio

Source: Table B.6-4, p119 of the submission; KN-001 Updated Data Tables p17-22; Table 12-21 p516-520 of CSR for KN-001, v01 full version

6.20 No statistical analyses of the pembrolizumab and ipilimumab data were presented in the submission. Known and unknown confounders influenced the comparisons. The known confounders identified included ECOG status: the majority of patients in part B1 and D of KN-001 (79.5%) had ECOG status equal to 0, while there was a 50:50 split in ECOG 0 and 1 status in Hodi 2010. This difference suggested a greater proportion of patients performing well in KN-001. Unknown confounders introduced by the comparisons made were that KN-001 was an uncontrolled phase 1 multi-cohort trial of a shorter duration than the single arm extracted from the comparative, randomised, double-blind trial of Hodi 2010. The PSCR subsequently included a subgroup analysis of KN-001 for the endpoint of ORR to claim that ECOG status is not a treatment effect modifier, but without providing a clear basis to judge confounding both of the comparative effectiveness against ipilimumab and also across other outcomes. The PSCR also included revised proportions of patients diagnosed across metastatic staging categories for pembrolizumab in KN-001 to claim that these proportions were similar to those for ipilimumab in Hodi 2010. The PSCR further argued that the differences in observed effect across the non-randomised pembrolizumab and ipilimumab groups were larger than might be explained by residual confounding.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

KN-002 data (received 24 November 2014)

6.21 The PBAC did not consider Trial KN-002 (at the May 2014 data cut) as a basis for deciding whether to recommend pembrolizumab for PBS listing because the trial was confined to ipilimumab-refractory patients and the sponsor subsequently revised its requested listing to exclude these patients. However, the PBAC did consider the results of KN-002 in the context of assessing the most appropriate dosage regimen for pembrolizumab.

**Comparison of 2 mg/kg Q3W and 10 mg/kg Q3W dose for PFS and OS**

KN-002 (ipi-refractory), May 2014 data cut	Pembrolizumab 2 mg/kg Q3W	Pembrolizumab 10 mg/kg Q3W	Hazard ratio (95% CI)	Chemotherapy <sup>b</sup>
N	180	181		179
<b>Progression-free survival (RECIST independent central review)</b>				
Median months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	0.91 (0.71, 1.16)	2.7 (2.5, 2.8)
PFS rate at 6 months	34%	38%		16%
<b>Overall survival<sup>a</sup></b>				
Median months (95% CI)	11.4 (10.2, -)	12.5 (9.7, -)	0.88 (0.63, 1.22)	

<sup>a</sup> Overall survival data for KN-002 were not supplied by the sponsor during the evaluation period (the report provided on 24 November 2014 stated that OS data are immature and pending the pre-specified analysis). The data presented here were provided in the PSCR.

<sup>b</sup> Chemotherapy regimens included: paclitaxel + carboplatin; paclitaxel; carboplatin; dacarbazine, temozolomide.

PFS=progression-free survival; Q2W=every 2 weeks; Q3W=every 3 weeks

Source: Ribas et al, presentation at the Society for Melanoma Research (SMR) 2014 International Congress Nov 13-16; Table 1, p1 of the tables included with the PSCR

6.22 The PSCR stated that data from the KN-002 trial demonstrates that there was a small increase in adverse events with the 10 mg/kg dose relative to the 2 mg/kg dose.

6.23 The PSCR (p7) also included statistical comparisons of PFS and OS for the 2 mg/kg Q3W and 10 mg/kg Q3W doses from the Part D (ipilimumab-naïve), Part B2 (ipilimumab-refractory) cohorts of KN-001. No significant differences were observed between doses, but no clear basis was provided to establish non-inferiority between these doses.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

KN-006 data (received 13 February 2015)

**Clinical trials**

6.24 The sponsor provided early results for trial KN-006, a phase III trial comparing pembrolizumab 10 mg/kg to ipilimumab after the finalisation of both the commentary on the submission and the ESC Advice. The following summarises the information provided, given that the results became the basis for PBAC decision making.

6.25 Details of Trial KN-006 are provided in the table below.

**Trials and associated reports presented after the ESC meeting**

Trial ID	Protocol title/ Publication title	Publication citation
KN-006	Interim analysis: early results report. First Interim Analysis of MK-3475 Phase III Advanced Melanoma Study (protocol 006-04). 09-Feb-2015	Unpublished

- 6.26 KN-006 is a randomised, open label phase III trial comparing pembrolizumab 10 mg/kg every 2 weeks (Q2W) for up to 2 years and 10 mg/kg every 3 weeks (Q3W) for up to 2 years with ipilimumab 3 mg/kg Q3W for 4 doses in the treatment of ipilimumab-naïve patients with unresectable or metastatic melanoma.

**Summary of KN-006**

Trial ID	N	Treatment arms	Trial design	Primary outcome	Use in the economic evaluation
KN-006	834	Pembro 10 mg/kg Q2W n=279	Phase III R, OL	PFS and OS	PSCR proposed use in a future model; no details of use provided
		Pembro 10 mg/kg Q3W n=277			
		Ipi 3 mg/kg Q3W n=278			

Ipi=ipilimumab; OL=open label; OS=overall survival; Pembro=pembrolizumab; PFS=progression-free survival; PSCR=Pre-Sub-Committee Response; Q2W=every 2 weeks; Q3W=every 3 weeks; R=randomised

Source: p35-36 of the interim analysis document

- 6.27 No crossover of the randomised therapies was permitted in the trial, however, the description of the management of crossover in the report did not clearly align with the corresponding description in Attachment 1 of the PSCR, which stated that a rank preserving structural failure time (RPSFT) model would be required “to control for receipt of non-study treatment (e.g. other PD-1 inhibitors) post-progression with ipilimumab (as pre-specified in the protocol)”. It appeared that efforts were made to minimise the use of ipilimumab or pembrolizumab when following trial participants after disease progression, but that the use of other post-progression medicines was not similarly constrained.
- 6.28 The trial report stated that the interim analysis was based on the February 2015 database lock and that results were virtually identical between the February 2015 data cut and the September 2014 data cut. All results provided in the report were labelled as the September 2014 data cut.
- 6.29 The table below provides baseline demographic data from KN-006.

**Summary of baseline demographic characteristics in KN-006**

	<b>Pembro 10 mg/kg Q2W N=279</b>	<b>Pembro 10 mg/kg Q3W N=277</b>	<b>Ipi 3 mg/kg Q3W N=278</b>
Age (mean years)	59.9	61.2	59.9
Gender (% male)	57.7%	62.8%	58.3%
Race (% Caucasian)	97.8%	97.8%	97.8%
ECOG n (%)			
0	196 (70.3%)	189 (68.2%)	188 (67.6%)
1	83 (29.7%)	88 (31.8%)	90 (32.4%)
BRAF mutation n (%)			
Mutant	98 (35.1%)	97 (35.0%)	107 (38.5%)
Wild type	177 (63.4%)	178 (64.3%)	170 (61.2%)
Unknown	4 (1.4%)	2 (0.7%)	1 (0.4%)
PD-L1 status			
Low	49 (17.6%)	53 (19.1%)	46 (16.5%)
High	219 (78.5%)	217 (78.3%)	223 (80.2%)
Missing	11 (3.9%)	7 (2.5%)	9 (3.2%)
Prior systemic therapy n (%)			
None	161 (57.7%)	165 (59.6%)	159 (57.2%)
Adjuvant	22 (7.9%)	20 (7.2%)	22 (7.9%)
First line	96 (34.4%)	91 (32.9%)	97 (34.9%)
Second line	0 (0.0%)	1 (0.4%)	0 (0.0%)

Ipi=ipilimumab; Pembro=pembrolizumab

Source: Table 2, p9-12 of the interim analysis document

- 6.30 The table below provides a summary of drug exposure at the interim analysis of KN-006. For patients treated with pembrolizumab, the mean exposure was 164 days in the 10 mg/kg Q2W arm and 151 days in the 10 mg/kg Q3W arm. The mean number of ipilimumab doses was 3.3 (limit of 4 doses), administered over approximately 50 days.
- 6.31 Median response duration was only reached for the 10 mg/kg Q2W dose of pembrolizumab (251 days). A reliable estimate of drug cost per patient could not yet be made.

**Drug exposure in KN-006**

	<b>Pembro 10 mg/kg Q2W N=279</b>	<b>Pembro 10 mg/kg Q3W N=277</b>	<b>Ipi 3 mg/kg Q3W N=256</b>
Days on therapy, mean (range)	163.93 (1 to 336)	151.45 (1 to 332)	49.89 (1 to 92)

Ipi=ipilimumab; Pembro=pembrolizumab

Source: Table 4, p26 of the interim analysis document

**Comparative effectiveness**

- 6.32 The table below provides a summary of progression-free and overall survival from KN-006.

**Progression-free and overall survival in KN-006 (September 2014 data cut)**

	<b>Pembro 10 mg/kg Q2W N=279</b>	<b>Pembro 10 mg/kg Q3W N=277</b>	<b>Ipi 3 mg/kg Q3W N=278</b>	<b>Absolute difference</b>	<b>HR (95% CI)</b>
<b>Progression-free survival (IRO review per RECIST 1.1)</b>					
Progressed	157 (56.3%)	157 (56.7%)	188 (67.6%)	10mg/kg Q2W vs. ipi: -11.3% 10mg/kg Q3W vs. ipi: -10.9%	-
Median mths (95% CI)	5.5 (3.4, 6.9)	4.1 (2.9, 6.9)	2.8 (2.8, 2.9)	10mg/kg Q2W vs. ipi: 2.7 10mg/kg Q3W vs. ipi: 1.3	0.58 (0.46, 0.72) 0.58 (0.47, 0.72)
PFS rate at 6 mths (%)	47.3% (41.2, 53.2)	46.4% (40.3, 52.3)	26.5% (20.9, 32.4)	10mg/kg Q2W vs. ipi: 20.8% 10mg/kg Q3W vs. ipi: 19.9%	-
<b>Progression-free survival (investigator evaluation per irRC<sup>a</sup>)</b>					
Progressed	142 (50.9%)	145 (52.3%)	177 (63.7%)	10mg/kg Q2W vs. ipi: -12.8% 10mg/kg Q3W vs. ipi: -11.4%	-
Median mths (95% CI)	7.0 (5.6, 9.6)	7.2 (5.6, 9.7)	3.3 (2.9, 4.2)	10mg/kg Q2W vs. ipi: 3.7 10mg/kg Q3W vs. ipi: 3.9	0.56 (0.45, 0.70) 0.56 (0.45, 0.70)
PFS rate at 6 mths (%)	54.5% (48.3, 60.3)	55.0% (48.8, 60.7)	33.6% (27.6, 39.7)	10mg/kg Q2W vs. ipi: 20.9% 10mg/kg Q3W vs. ipi: 21.4%	-
<b>Overall survival</b>					
Died	61 (21.9%)	56 (20.2%)	85 (30.6%)	10mg/kg Q2W vs. ipi: -8.7% 10mg/kg Q3W vs. ipi: -10.4%	
Median mths (95% CI)	NR	NR	NR	10mg/kg Q2W vs. ipi: - 10mg/kg Q3W vs. ipi: -	0.60 (0.43, 0.84) 0.56 (0.40, 0.78)
OS rate at 6 mths (%)	84.8% (80.0%, 88.5%)	87.6% (83.1%, 91.0%)	74.6% (68.8%, 79.5%)	10mg/kg Q2W vs. ipi: 10.2% 10mg/kg Q3W vs. ipi: 13.0%	

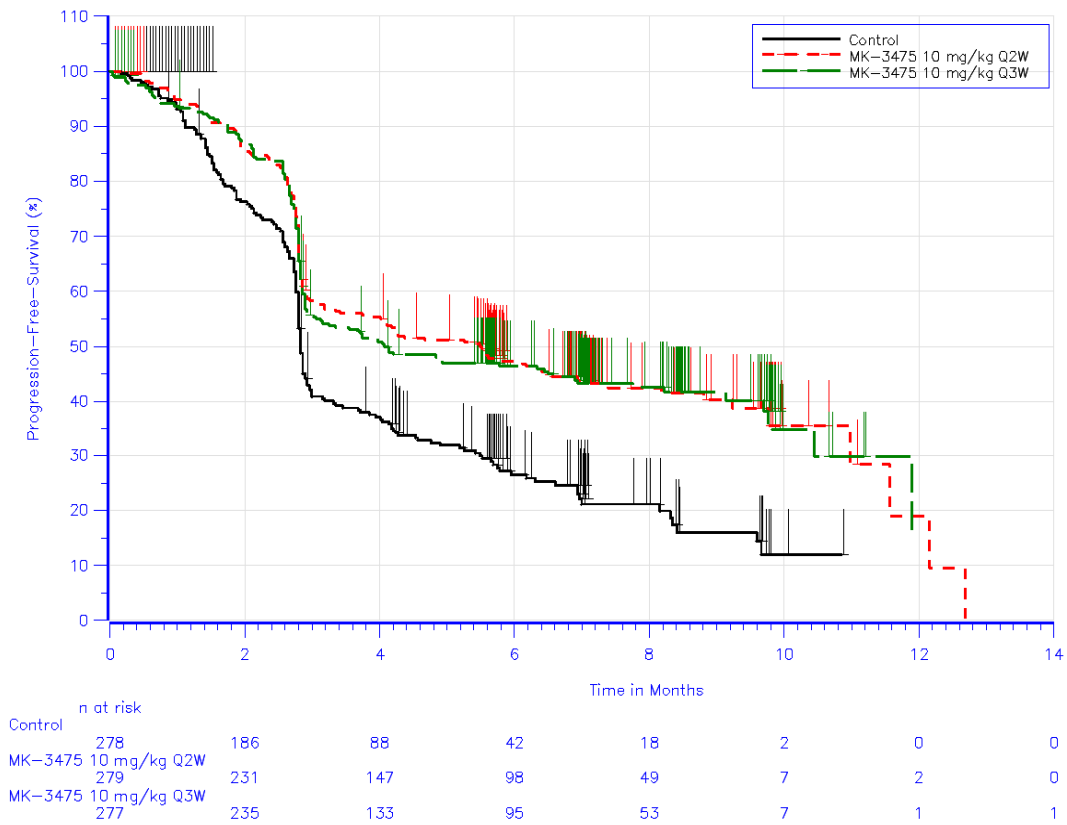
<sup>a</sup> The interim report states that irRC differs from RECIST 1.1 in that progression of disease generally requires confirmation at least 4 weeks after an initial assessment (unless the patient has rapid or symptomatic disease progression based on clinical judgment and is unsuitable to wait for confirmation of progression). In addition, new lesions are counted into the total disease burden in irRC and do not automatically trigger an assessment of disease progression as in RECIST 1.1.

Ipi=ipilimumab; IRO=independent radiologist plus oncologist's review (defined in the submission for KN-001 as integrated radiology and oncology assessment, which is the same as independent central review reported in KN-001); irRC=immune-related response criteria; NR=not reached; OS=overall survival; Pembro=pembrolizumab; PFS=progression-free survival

Source: Table 3, p13; Table 1, p15; Table 5, p17 of the interim analysis document

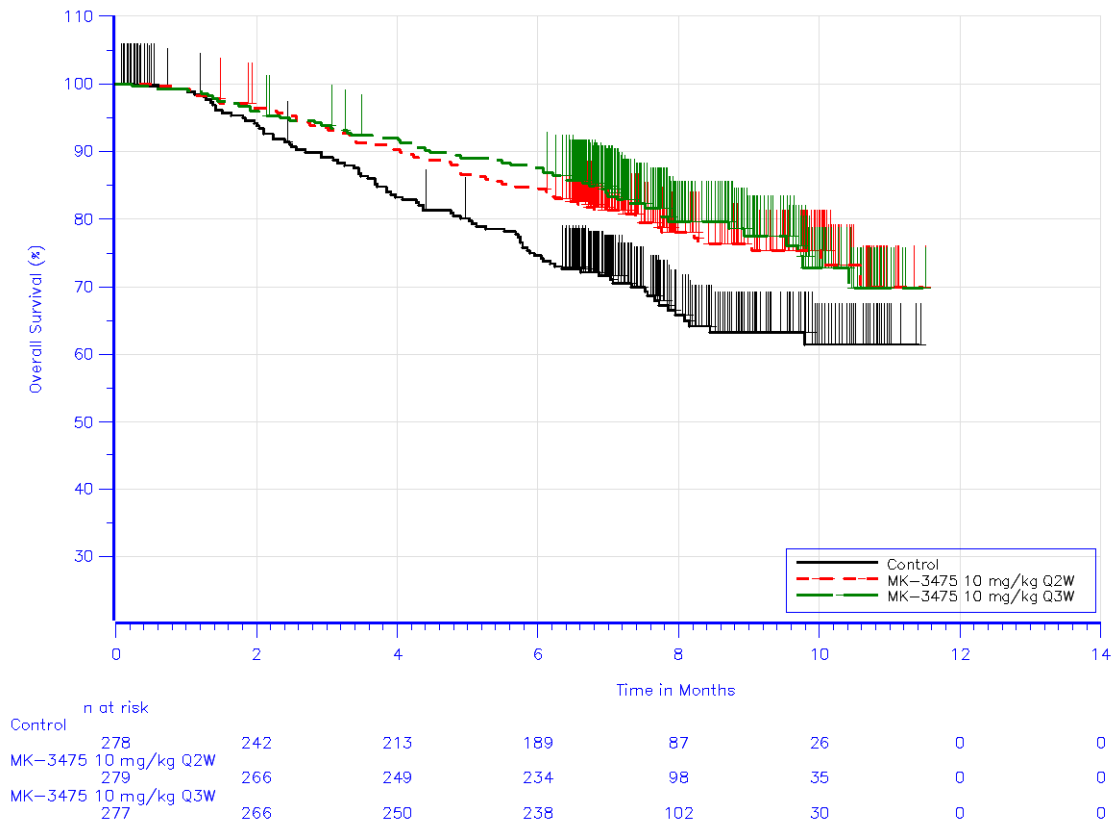
6.33 The Kaplan-Meier plots of PFS and OS are provided in the figures below.

Kaplan-Meier PFS curves (September 2014 data cut)



Source: Figure 1, p14 of the interim analysis document

Kaplan-Meier OS curves (September 2014 data cut)



Source: Figure 3, p18 of the interim analysis document

- 6.34 Both 10 mg/kg doses of pembrolizumab showed statistically significantly longer PFS compared to ipilimumab. The median months of PFS were longer using the immune-related response criteria (irRC) assessment. The interim report stated that irRC differs from RECIST 1.1 in that progression of disease generally requires confirmation at least 4 weeks after an initial assessment and new lesions are counted into the total disease burden in irRC and do not automatically trigger an assessment of disease progression as in RECIST 1.1.
- 6.35 Median overall survival was not reached in any arm of KN-006 and was not statistically significant at the pre-specified alpha level of 0.00002 that would warrant early stopping for efficacy. The interim report stated that the OS data is not mature at the first interim analysis, which had a median OS follow-up of approximately 8 months. The report indicated that a second interim analysis will be performed when the minimum follow-up is 9 months and 290 deaths have occurred, or will be performed when minimum follow-up is 12 months if it takes longer than 12 months of follow-up to observe 290 deaths. The report stated that it is projected that the second interim analysis will begin on 3 March 2015 when there is a minimum of 12 months of follow-up. The final analysis of OS will take place when 435 deaths have occurred or when all patients have been followed for 21 months, whichever occurs first.

- 6.36 Overall response rate (ORR), time to response and response duration are summarised in the table below. There was a significantly greater ORR in both the pembrolizumab 10 mg/kg Q2W group (proportion difference=16.1%; 95% CI: 7.8%, 24.5%) and 10 mg/kg Q3W group (proportion difference=17.2%; 95% CI: 9.5%, 25.6%) compared to patients treated with ipilimumab. Median response duration was only reached in the 10 mg/kg Q2W group treated with pembrolizumab (days=251; range: 42+, 251).

**Summary of ORR, time to response and response duration in KN-006 (September 2014 data cut)**

	Pembro 10 mg/kg Q2W N=279	Pembro 10 mg/kg Q3W N=277	Ipi 3 mg/kg Q3W N=278	Difference in % <sup>a</sup> (95% CI)	
				10 mg/kg Q2W vs. ipi	10 mg/kg Q3W vs. ipi
Number of overall responses	94	91	33	-	
ORR % (95% CI)	33.7% (28.2, 39.6)	32.9% (27.4, 38.7)	11.9% (8.3, 16.3)	16.1 (7.8, 24.5)	17.2 (9.5, 25.6)
Ongoing response n (%)	84 (89%)	88 (97%)	29 (88%)	Not reported	
Median time to response days (range)	86 (32-212)	85 (36-251)	87 (80-250)	Not reported	
Median response duration days (range)	251 (42+, 251)	NR (42+, 246+)	NR (33+, 239+)	Not reported	

<sup>a</sup> Based on Miettinen & Nurminen method stratified by line of therapy (1<sup>st</sup> vs. 2<sup>nd</sup>), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1).

Ipi=ipilimumab; NR=not reached; ORR=overall response rate; Pembro=pembrolizumab

Source: Table 2, p27; Table 7, p29-30 of the interim analysis document

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

### **Comparative harms**

- 6.37 The table below summarises adverse event data provided for KN-006.

**Summary of adverse events in KN-006 (September 2014 data cut)**

Adverse event	Pembro 10 mg/kg Q2W N=278	Pembro 10 mg/kg Q3W N=277	Ipi 3 mg/kg Q3W N=256	Difference in % <sup>a</sup> (95% CI)	
				10 mg/kg Q2W vs. ipi	10 mg/kg Q3W vs. ipi
Grade 3-5 drug-related AE	37 (13.3%)	28 (10.1%)	51 (19.9%)	NR	NR
Sponsor-defined events of clinical interest	126 (45.3%)	122 (44.0%)	127 (49.6%)	-9.9 (-21.7, 2.3)	-14.1 (-25.4, -2.4)
Grade ≥3 hyper or hypothyroidism, hypophysitis or any grade resulting in dose modification	3 (1.1%)	5 (1.8%)	4 (1.6%)	-0.4 (-2.9, 1.4)	0.4 (-2.6, 2.9)
Grade ≥2 pneumonitis	1 (0.4%)	4 (1.4%)	1 (0.4%)	-0.2 (-3.3, 2.6)	1.5 (-1.3, 5.1)
Grade ≥3 rash or any grade resulting in dose modification	2 (0.07%)	3 (1.1%)	6 (2.3%)	-2.2 (-6.6, 0.7)	-2.0 (-6.3, 1.3)
Grade ≥2 renal event or any grade resulting in dose modification	2 (0.7%)	4 (1.4%)	4 (1.6%)	-0.4 (-2.7, 1.2)	0.5 (-2.2, 2.9)
Grade ≥2 uveitis or iritis or any grade resulting in dose modification	1 (0.4%)	2 (0.7%)	0 (0.0%)	0.7 (-2.3, 4.0)	0.4 (-2.3, 3.3)
Grade ≥2 hepatitis or any grade resulting in dose modification	3 (1.1%)	4 (1.4%)	1 (0.4%)	0.2 (-2.3, 2.9)	0.4 (-2.0, 3.0)
Investigator-assessed immune related AE	114 (41.0%)	109 (39.4%)	110 (43.0%)	-3.4 (-14.1, 6.7)	-4.4 (-15.4, 6.0)

<sup>a</sup> Based on Miettinen & Nurminen method stratified by line of therapy (1<sup>st</sup> vs. 2<sup>nd</sup>), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1).

Ipi=ipilimumab; NR=not reported; Pembro=pembrolizumab

Source: Table 5, p27; Table 7, p29-30 of the interim analysis document

- 6.38 With the exception of ‘sponsor-defined events of clinical interest’, which showed significantly fewer adverse events with pembrolizumab 10 mg/kg Q3W compared to ipilimumab, there were no statistically significant differences in the adverse events presented in the interim report.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Benefits/harms**

- 6.39 A summary of benefits and harms is presented below using the data from KN-006.

**Summary of benefits and harms for pembrolizumab and ipilimumab**

	Pembrolizumab 10 mg/kg Q2W N=279	Pembrolizumab 10 mg/kg Q3W N=277	Ipilimumab 3 mg/kg Q3W N=278	Difference in % <sup>a</sup> (95% CI)	
				10 mg/kg Q2W vs. ipilimumab	10 mg/kg Q3W vs. ipilimumab
<b>Benefits</b>					
<b>Overall responses</b>					
Number	94	91	33	-	
ORR % (95% CI)	33.7% (28.2, 39.6)	32.9% (27.4, 38.7)	11.9% (8.3, 16.3)	16.1 (7.8, 24.5)	17.2 (9.5, 25.6)
	Pembrolizumab 10 mg/kg Q2W N=279	Pembrolizumab 10 mg/kg Q3W N=277	Ipilimumab 3 mg/kg Q3W N=278	Absolute difference	HR (95% CI)
<b>Progression-free survival (IRO review per RECIST 1.1)</b>					
Median mths (95% CI)	5.5 (3.4, 6.9)	4.1 (2.9, 6.9)	2.8 (2.8, 2.9)	10mg/kg Q2W vs. ipi: 2.7 10mg/kg Q3W vs. ipi: 1.3	0.58 (0.46, 0.72) 0.58 (0.47, 0.72)
PFS rate at 6 months	47.3% (41.2, 53.2)	46.4% (40.3, 52.3)	26.5% (20.9, 32.4)	10mg/kg Q2W vs. ipi: 20.8% 10mg/kg Q3W vs. ipi: 19.9%	-
<b>Progression-free survival (investigator evaluation per irRC<sup>b</sup>)</b>					
Median mths (95% CI)	7.0 (5.6, 9.6)	7.2 (5.6, 9.7)	3.3 (2.9, 4.2)	10mg/kg Q2W vs. ipi: 3.7 10mg/kg Q3W vs. ipi: 3.9	0.56 (0.45, 0.70) 0.56 (0.45, 0.70)
PFS rate at 6 mths (%)	54.5% (48.3, 60.3)	55.0% (48.8, 60.7)	33.6% (27.6, 39.7)	10mg/kg Q2W vs. ipi: 20.9% 10mg/kg Q3W vs. ipi: 21.4%	-
<b>Overall survival</b>					
Median mths (95% CI)	NR	NR	NR	10mg/kg Q2W vs. ipi: - 10mg/kg Q3W vs. ipi: -	0.60 (0.43, 0.84) 0.56 (0.40, 0.78)
OS rate at 6 mths (%)	84.8% (80.0%, 88.5%)	87.6% (83.1%, 91.0%)	74.6% (68.8%, 79.5%)	10mg/kg Q2W vs. ipi: 10.2% 10mg/kg Q3W vs. ipi: 13.0%	
<b>Harms</b>					
	Pembrolizumab 10 mg/kg Q2W N=279	Pembrolizumab 10 mg/kg Q3W N=277	Ipilimumab 3 mg/kg Q3W N=278	Difference in % <sup>a</sup> (95% CI)	
				10 mg/kg Q2W vs. ipilimumab	10 mg/kg Q3W vs. ipilimumab
Sponsor-defined events of clinical interest	126 (45.3%)	122 (44.0%)	127 (49.6%)	-9.9 (-21.7, 2.3)	-14.1 (-25.4, -2.4)

<sup>a</sup> Based on Miettinen & Nurminen method stratified by line of therapy (1<sup>st</sup> vs. 2<sup>nd</sup>), PD-L1 status (high positive vs. low positive) and ECOG (0 vs. 1).

<sup>b</sup> The interim report states that irRC differs from RECIST 1.1 in that progression of disease generally requires confirmation at least 4 weeks after an initial assessment (unless the patient has rapid or symptomatic disease progression based on clinical judgment and is unsuitable to wait for confirmation of progression). In addition, new lesions are counted into the total disease burden in irRC and do not automatically trigger an assessment of disease progression as in RECIST 1.1.

IRO=independent radiologist plus oncologist's review (defined in the submission for KN-001 as integrated radiology and oncology assessment, which is the same as independent central review reported in KN-001); irRC=immune-related response criteria; NR=not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

Source: Table 3, p13; Table 1, p15; Table 5, p17; Table 7, p29-30 of the interim analysis document

6.40 On the basis of the early KN-006 data with a median follow-up of approximately eight months, for every 100 patients treated with pembrolizumab compared with ipilimumab:

- 10-13 more patients will be alive at 6 months
- 20-21 more patients will not have progressed at 6 months
- 16-17 more patients will have experienced a response
- 10-14 fewer patients will have a sponsor-defined event of clinical interest.

### **Clinical claim**

- 6.41 The interim analysis report of KN-006 stated that the data demonstrate that pembrolizumab improves PFS and OS of ipilimumab-naïve patients compared to ipilimumab, and that pembrolizumab has a favourable safety profile on major categories of adverse events in comparison to ipilimumab.
- 6.42 Although the interim results of KN-006 provide comparative evidence versus ipilimumab, and there is evidence of statistically significant improvement in PFS for pembrolizumab-treated patients, the following concerns remained:
- KN-006 used two regimens of the 10 mg/kg dose of pembrolizumab while registration in Australia has only been sought for the 2 mg/kg dose. Evidence provided in the submission and the PSCR did not adequately demonstrate the equivalence of the 2 mg/kg and 10 mg/kg doses, particularly for safety.
  - Overall survival data had not yet reached maturity and no statistically significant difference was observed at the trial's pre-specified level for an interim analysis.
  - Given the recent availability of the KN-006 data, the comparative results versus ipilimumab were not yet applied in an economic evaluation.
- 6.43 The PBAC considered that the claim of superior comparative effectiveness of pembrolizumab over ipilimumab was probably reasonable, but noted that the extent of incremental effectiveness and duration of benefit could not be estimated with confidence given the limitations of the current evidence base.
- 6.44 The PBAC concluded that pembrolizumab is no worse than ipilimumab in terms of safety, and possibly less toxic.

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

### **Economic analysis**

#### Original submission (5 November 2014)

- 6.45 The submission presented a modelled cost-utility analysis. The clinical evidence presented in the submission was used in the economic model despite its many limitations, which did not support a cost-utility analysis.

**Summary of model structure and rationale**

Component	Summary
Time horizon	5 years in the base case versus 3.1 to 8.7 months across KN-001 cohorts.
Outcomes	Quality-adjusted life-years (QALYs)
Methods used to generate results	Partitioned survival analysis using piece-wise fitting of exponential functions
Health states	Progression free (referred to in the submission model as PFS) Progression (referred to in the submission model as post-PD) Death
Cycle length	1 week
Transition probabilities (i.e. distributions; explicit transition probabilities not used)	Ipilimumab: Cumulative hazard figures in Dickson 2011 based on Hodi 2010 were digitised and fitted in piece wise exponential function parameters using the gamlss package within R for PFS and separately for OS. Pembrolizumab: Piece-wise exponential functions were estimated from pooled data for ipilimumab-naïve patients (2 mg/kg Q3W, 10 mg/kg Q2W, and 10 mg/kg Q3W) in KN-001 for PFS and separately for OS.

Source: compiled during the evaluation

- 6.46 Key drivers of the model are identified in the table below.

**Key drivers of the model**

Description	Method/Value	Impact
Estimate of OS	The estimate of incremental OS for pembrolizumab over ipilimumab is unreliable given the available data and the modelling methods used	High, favours pembrolizumab
Utility values	The utility value of post-PD in particular	Moderate, favours pembrolizumab

OS=overall survival; PD=progressive disease

Source: compiled during the evaluation

- 6.47 The results of the modelled evaluation are provided in the table below.

**Results of the economic evaluation**

Component	Pembrolizumab	Ipilimumab	Increment
Costs	\$ [REDACTED]	\$130,761	\$ [REDACTED]
QALYs	1.91	1.12	0.79
<b>Incremental cost/extra QALY gained</b>			\$ [REDACTED]

Source: Table D.5.8, p.216 of the submission

- 6.48 The submission used ex-manufacturer prices of pembrolizumab and ipilimumab in the model. Each price was converted during the evaluation to the corresponding dispensed price for maximum amount (DPMA).

**Pre-Sub-Committee Response (received 28 January 2015)**

- 6.49 The results of the modelled evaluation as updated in the PSCR are provided in the table below. The main change made to the revised model reported in the PSCR was the convergence of the OS curves for pembrolizumab and ipilimumab at 10 years instead of 40 years as in the submission. This increased the sponsor's ICER estimate from \$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$75,000/QALY (using DPMA).

**Results of the economic evaluation – submission and PSCR**

Component	Pembrolizumab	Ipilimumab	Increment
<b>Model results from the submission</b>			
Costs <sup>a</sup>	\$ [REDACTED]	\$130,761	\$ [REDACTED]
QALYs	1.91	1.12	0.79
<b>Incremental cost/extra QALY gained</b>			\$ [REDACTED]
<b>Model results from the PSCR</b>			
Costs <sup>a</sup>	\$ [REDACTED]	\$130,950	\$ [REDACTED]
QALYs	1.84	1.12	0.72
<b>Incremental cost/extra QALY gained</b>			\$ [REDACTED]
<b>Sensitivity analyses from the PSCR</b>			<b>ICER<sup>a</sup></b>
OS curves converge at 5 years (base case 10 years)			\$ [REDACTED]
95% CI of pembrolizumab OS hazard (0.005148, 0.006516)			\$ [REDACTED]
Range of OS hazard of ipilimumab, based on point estimate of the hazard and the 95% CI of the hazard ratio over glycoprotein 100 peptide vaccine			\$ [REDACTED] - \$ [REDACTED]
Hazards of both pembrolizumab and ipilimumab (upper and lower 95% confidence limits)			\$ [REDACTED] - \$ [REDACTED]
Range of ipilimumab usage post pembrolizumab (0-20%)			\$ [REDACTED] - \$ [REDACTED]

<sup>a</sup> Ex-manufacturer cost of \$ [REDACTED] per cycle for pembrolizumab and \$31,351.58 per cycle for ipilimumab changed to DPMA cost of \$ [REDACTED] per cycle for pembrolizumab and \$31,793.74 per cycle for ipilimumab.

Source: Table D.5.8, p.216 of the submission and p5 PSCR

6.50 The ICER estimated by the model did not accurately represent the cost-effectiveness of pembrolizumab given the following problems with the model:

- Structural problems: inappropriate application of all-cause mortality and inconsistency with the expected pembrolizumab treatment algorithm. In relation to the latter, the ESC noted that assuming the use of ipilimumab after pembrolizumab in 20% of patients as per the sensitivity analysis in the PSCR increased the ICER for the revised model in the PSCR to \$75,000/QALY - \$105,000/QALY.
- Methodological problems: PFS and OS data used in the model were based on fitted values only. The submission did not apply the available trial data (to the most recent April 2014 data cut) and then extrapolate. The ESC noted that simultaneously using the upper 95% confidence limits for the pembrolizumab and ipilimumab hazards and simultaneously using the lower 95% confidence limits for the pembrolizumab and ipilimumab hazards gave an ICER range for the revised model in the PSCR of \$45,000/QALY - \$75,000/QALY to \$75,000/QALY - \$105,000/QALY. Estimates of PFS and OS produced by the model were not consistent with the stated timeframe of the model and increased the incremental benefit favouring pembrolizumab. The ESC noted that also converging the OS curves by 5 years increased the ICER for the revised model in the PSCR to \$45,000/QALY - \$75,000/QALY.
- Content problems: disease management costs estimated from the INTUITION study was not representative of Australian patients on ipilimumab and pembrolizumab in the model.

6.51 A particular concern with the model was that the projected incremental OS remained unreliable and was likely to be significantly overstated. Importantly, the revised base case still assumed convergence of OS beyond the 5-year time horizon of the model (reduced to 10 years for the revised model compared with 40 years for the original model). Therefore, even if the early data for PFS and OS in the model were

considered reliable, this approach still significantly overstated the modelled incremental OS.

- 6.52 The submission did not provide any sensitivity analyses using 95% CIs for OS values for the original model. The PSCR provided 95% confidence intervals for the revised model. In lieu of testing the 95% CI for incremental OS, and to explore the sensitivity of lambda values<sup>2</sup> in the fitted OS functions, sensitivity analyses conducted during the evaluation varied the lambda values. A 20% reduction in the value of lambda in the OS function for ipilimumab combined with a 20% increase in the value of lambda in the OS function for pembrolizumab resulted in an ICER of \$75,000/QALY - \$105,000/QALY. The PSCR also presented a sensitivity analysis assuming that up to 20% of pembrolizumab patients might be treated with ipilimumab. This analysis increased the ICER to \$75,000/QALY - \$105,000/QALY from the revised base case of \$45,000/QALY - \$75,000/QALY.
- 6.53 The revised model's approach to all-cause mortality still underestimated true all-cause mortality because the model did not allow for the background rate of all-cause mortality to increase with age over the duration of the model. This further inflated the overestimation of incremental OS in the model, with increasing consequence if the convergence of OS increases from 5 years to 10 years and to 40 years.
- 6.54 The PFS and OS data used in the revised model were still based on fitted data only. The PSCR argued that the fit of the functions was relatively good. The PSCR stated that the sponsor would be prepared to revise the model further, by applying Kaplan-Meier data until it became unreliable (proposed to be where 20% of patients or 20 patients (whichever is less) are remaining at risk) and then only apply parametric functions beyond this time point.
- 6.55 The structure of the revised model remained inconsistent with the treatment algorithm because patients failing pembrolizumab do not receive ipilimumab. This assumption was only examined in a sensitivity analysis.
- 6.56 Additionally, the cost of pembrolizumab during the induction phase was still understated in the model because patients with progressive disease in the model discontinue therapy even though the first assessment of PFS only occurs at 12 weeks (4 cycles) and patients are encouraged to complete all 4 cycles.
- 6.57 The populations modelled from KN-001 and Hodi 2010 appeared to be different. As noted above, Hodi 2010 recruited patients who had poorer performance and poorer prognosis, favouring pembrolizumab. A model based on KN-006 data would remove this issue.
- 6.58 With the exception of the identification of all reported patients in the INTUITION study being from Australia, the PSCR provided neither adequate explanation nor referencing in relation to estimation of resource use. Consequently, the model still lacked transparency in the estimation of cost parameters.

---

<sup>2</sup> Definitional note: 'lambda value' refers to the exponential parameter that determines the shape of the survival function in a modelled economic evaluation.

- 6.59 The source of adverse events used in the revised model remained the same as those in the submission's original model. The PSCR stated that the adverse event rates were taken from the April 2014 data cut for Part B1 and Part D of KN-001. This was incorrect. The adverse event rates in the revised model were not changed from those used in the submission. These rates were provided in Table D.4-4, p199 of the submission and were sourced from the October 2013 data cut of KN-001 and were based on the Part B1 (ipilimumab-naïve and ipilimumab-treated), Part B2 (ipilimumab-refractory) and Part D (ipilimumab-naïve) cohorts of KN-001. Importantly, these events were based on a different population than that used for the efficacy parameters.
- 6.60 The table below shows the consequences for key incremental results of moving from the submission's original base case to the PSCR revised base case, and also to the 5-year OS convergence scenario in the PSCR's sensitivity analysis. This table shows that, compared to the original base case:
- incremental costs were decreased, but only slightly (due to fewer survivors remaining on long-term therapy)
  - incremental PFS remained unchanged. The original model assumed convergence of OS at 40 years and PFS at 5 years. However, if OS was now assumed in the revised model to converge at either 10 years or 5 years, it seemed improbable that PFS would not be reduced as well
  - incremental LYS and QALYs were decreased.

**Incremental impacts across the submission's model and the revised PSCR model**

	Submission base case 40-year OS convergence	PSCR base case 10-year OS convergence	PSCR sensitivity analysis 5-year OS convergence
Cost increment <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
PFS increment	0.61	0.61	0.61
Post-PD increment	0.52	0.42	0.22
LYS increment	1.01	0.92	0.76
QALY increment	0.79	0.72	0.60

<sup>a</sup> Results for DPMA costs

PD=progressive disease; PSCR=Pre-Sub-Committee Response

Source: compiled from the submission and the PSCR

- 6.61 The PSCR indicated that a proposed MES should include the specification of a model that could be used to review the cost-effectiveness of pembrolizumab versus ipilimumab when data from KN-006 are available. The PSCR suggested that the finalisation of the model, including identification of appropriate inputs for the model both now and as part of the MES framework could be performed in consultation with the evaluator and/or a Departmental officer prior to PBAC consideration.

Pre-PBAC response (4 March 2015)

- 6.62 The pre-PBAC response did not use the availability of directly comparative data (trial KN-006) to further update the modelled evaluation. Instead, the pre-PBAC response proposed that the base case of the revised model presented in the PSCR should be used for decision-making, with its ICER of \$45,000/QALY - \$75,000/QALY (corrected to DPMA), and also presented additional sensitivity analyses for this revised model.
- 6.63 Consequently, there was no estimate of the cost-effectiveness of pembrolizumab

based on the available comparative data from KN-006.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

**Drug cost/patient/course:** no reliable estimate could be made.

6.64 Given the inadequacy of the available evidence, a reliable estimate of drug cost per patient could not be made. Several values were possible. Basing drug cost on the PFS in the cohorts of KN-001 resulted in an estimate of drug cost ranging from \$ [redacted] (3.1 months median PFS) to \$ [redacted] (8.7 months median PFS), assuming a drug cost of \$ [redacted] per cycle. If the estimate of mean PFS from the model was used (14.34 months), then the cost per treatment course would be \$ [redacted]. Median response duration was not reached for most cohorts, with data only available for the 10 mg/kg Q3W dose in the combined Part B1 plus D cohort. Median response reported in the submission and clinical study report (CSR) for this cohort was 93 weeks, with a range of 6 to 93 weeks. Using this source, the drug cost per patient per course would range from \$ [redacted] to \$ [redacted].

For more detail on PBAC’s view, see section 7 “PBAC outcome”

**Estimated PBS usage & financial implications**

6.65 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the extent of use and financial implications of listing pembrolizumab for the treatment of unresectable (stage III) or metastatic (stage IV) melanoma. The PSCR provided financial estimates based on the assumption that 12% of patients treated with pembrolizumab would subsequently receive ipilimumab. These estimates could not be verified, but are provided in the table below.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vials (50 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Rebate <sup>b</sup>	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Total cost of ipilimumab	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Revised net cost to PBS/RPBS*	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to MBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>Estimated total net cost</b>					
Net cost to PBS/RPBS/MBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Revised net cost to PBS/RPBS/MBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

<sup>a</sup> Includes 1,417 non-grandfathered patients and 445 grandfathered patients.

<sup>b</sup> [redacted]% rebate on the ex-manufacturer drug cost to be applied to incremental use beyond [redacted] years.

\* As provided in the PSCR, assuming 12% of pembrolizumab-treated patients would subsequently receive ipilimumab.

Source: Table E.4-1, p255; Table E.5-5 - Table E.5-7, p255-260 of the submission

- 6.66 The redacted table above shows that less than 10,000 patients are expected to be treated with pembrolizumab per year at a net cost of between \$50,000,000 and \$150,000,000 per year.
- 6.67 The estimated net costs were not likely to be accurate as the expected treatment duration for pembrolizumab was based on estimates from the economic model, which utilised inappropriate extrapolations of progression free survival.

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

### **Quality Use of Medicines**

- 6.68 The submission proposed a number of activities to support the quality use of medicines, including development of educational materials and activities; support workshops of specialists; guidance documentation for identification of adverse events (primarily those that are immune-related); and funding to assist national health consumer organisations to update patient information materials.
- 6.69 The pre-PBAC response proposed that any patients who were on ipilimumab prior to pembrolizumab listing and who become refractory to treatment would be provided pembrolizumab by the sponsor through a compassionate access program. Further details were provided in a late document received on 6 March 2015.

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

### **Financial Management – Risk Sharing Arrangement**

- 6.70 The sponsor proposed that pembrolizumab be reimbursed under a Deed of Agreement (DOA). Clinical uncertainty would be addressed through a managed entry scheme (MES) framework (see below), and financial uncertainty addressed through a risk sharing arrangement (RSA).
- 6.71 In order to address financial uncertainty associated with duration of treatment, the submission proposed a ■% rebate on the ex-manufacturer drug cost for incremental use beyond ■ years. While identified as part of the MES proposal, this falls under the frequently encountered RSA framework for a DOA, and is a separate type of agreement to an MES. The RSA rebate was incorporated into the financial estimates and economic model (rebate of \$■ to \$■ from year 3 to 5). Given that the amount of the rebate is based on treatment duration sourced from extrapolations of PFS in the economic model that were considered to be highly unreliable, it is not likely the proposed rebate is accurate.

### **Sponsor's proposed MES for ipilimumab-naïve patients**

- 6.72 In order to address clinical uncertainty in an MES framework, an interim 'uncertainty discount' was offered. In an example provided in the submission, adjustment to the pembrolizumab price would occur upon provision of 3-year OS data from trial KN-001 (available in April 2016). The submission indicated that the exact magnitudes of changes for the undisclosed discount were open for negotiation following a positive

PBAC recommendation. The table below provides the example framework proposed by the submission.

**Example of proposed MES framework for pembrolizumab**

KN-001: OS rate at 3 years (available April 2016)		Change to undisclosed discount (illustrative purposes only)
Ipilimumab	Pembrolizumab	
18%	<10%	-13%
	10-25%	0%
	26-35%	+13%
	>35%	+25%

Source: Table F.2.1, p272 of the submission

- 6.73 The ‘uncertainty discount’ as proposed by the submission was not considered to constitute a feasible MES framework, for the following reasons:
- More mature (3-year) non-comparative OS data from KN-001 could not address the biases observed in the comparison based on KN-001.
  - The submission assumed that the new price discount would reflect the proposed ICER of [REDACTED] for a given pembrolizumab 3-year OS rate. This assumption did not recognise that the ICER produced by the submission’s model was not reliable given structural, methodological and content issues.
  - The MES proposal did not acknowledge that a high initial price was sought without demonstrated cost-effectiveness and did not set up appropriate consideration of future evidence.
- 6.74 A revised MES proposal was provided as Attachment 1 of the PSCR. The table below summarises uncertainties which were aimed to be addressed through the MES and the expected data to be used to resolve each issue.

**Summary of revised MES proposal attached to the PSCR preparing for a future review of the cost-effectiveness of pembrolizumab**

Uncertainty	How it will be addressed by MES
Magnitude of incremental benefit of pembrolizumab over ipilimumab	Outcomes from KN-006
Proportion of patients using ipilimumab after pembrolizumab	Analysis of post-progression treatment KN-006
Preference weights to be applied to health states	EQ-5D data from KN-006
Disease management costs	INTUITION final analysis; health care resource use collected in KN-006, clinical expert input
Structure of economic model	Not detailed
Inputs to calculate ICER	Costs over 1 <sup>st</sup> and 2 <sup>nd</sup> years of therapy with [REDACTED] % discount to costs of pembrolizumab for continuous treatment of a patient beyond [REDACTED] years Agreed estimate of average duration of therapy, estimate of QALYs gained over ipilimumab and ICER threshold that represents cost effectiveness
Time point for review of cost-effectiveness	Analyses of KN-006 within 2 years of listing
Inputs to be provided at time of review	Final analysis of KN-006 due Q2 2016 including efficacy, safety, medicine use, preference weight (EQ-5D), subgroup analysis, healthcare resources
Analysis of PBS data	Utilisation of ipilimumab (including post-progression)
Supportive analysis for long-term predictions of PFS and OS	KN-001 Part D and Hodi 2010

Source: PSCR, Attachment 1, p5-7

- 6.75 The ESC considered that the proposed managed entry scheme should be built around the ongoing randomised, controlled, therapeutic confirmatory multi-centre trial in ipilimumab-naïve patients (KN-006) with its stated co-primary endpoints of progression-free survival and overall survival.
- 6.76 The MES proposal in the pre-PBAC response set out an initial listing and an initial price, followed by a proposed review of new evidence from the completed KN-006 trial and associated revised economic modelling to determine any revision to the initial listing and price.
- 6.77 The pre-PBAC response indicated that the initial price would include an uncertainty discount, calculated by using a sensitivity analysis with a less favourable outcome giving an ICER of \$75,000/QALY - \$105,000/QALY (using the requested ex-manufacturer price of pembrolizumab), and reducing the initial pembrolizumab price so that this less favourable ICER equalled its corresponding base case ICER of \$45,000/QALY - \$75,000/QALY.
- 6.78 For the reconsideration of new evidence and modelling generated during the MES period, the pre-PBAC response indicated that it would a) not apply the uncertainty discount and b) apply a retrospective price adjustment. The PBAC rejected the proposal for any subsequent higher price to apply retrospectively, noting that this would not be consistent with the intent of the MES framework.
- 6.79 The PBAC considered that the pivotal clinical uncertainty to be addressed in the MES was the magnitude of life extension that would be gained in addition to the expected quality of life improvement that would be gained through delays in disease progression. The PBAC agreed with the ESC that, when it is completed, the KN-006 trial would offer the most rigorous basis to address this uncertainty. However, the PBAC noted that the post-progression results of the completed KN-006 trial might be contaminated by patients either withdrawing from the trial to receive post-trial pembrolizumab or by patients switching to other therapies for melanoma. Given this risk of contamination, the PBAC advised that the clinical and economic evaluations using the completed KN-006 trial should be based on the standard ITT analysis. The PBAC considered that the survival analysis should not be adjusted to account for contamination because the Committee was not convinced that adjustment methods could be relied upon, even if they are prespecified.
- 6.80 The PBAC considered that because of fundamental problems with the versions of the model submitted to form the basis of an initial price (see paragraph 7.18 below), the economic model to be presented at the end of the MES using the completed KN-006 trial data should be substantially modified.
- 6.81 The PBAC therefore was not satisfied with the MES proposed in the submission, and instead proposed a modified MES which would address the uncertainty related to the magnitude of clinical benefit. The PBAC agreed that the modified MES scheme would provide early access to ipilimumab-naïve patients for whom there is a high clinical need.

### **PBAC-proposed MES**

6.82 The PBAC considered that the MES for pembrolizumab should be guided by the following.

- The initial price of pembrolizumab for PBS listing would be determined on the basis of the current cost per patient to the PBS of ipilimumab at its effective price. Rather than a direct price reduction, this would be achieved by setting the RSA expenditure caps for pembrolizumab with reference to the average cost of ipilimumab per patient using appropriate historical PBS dispensing data, and the revised utilisation estimates based on current ipilimumab utilisation via the PBS. These data indicated that approximately [REDACTED] patients have commenced ipilimumab each year, with an average of [REDACTED] induction doses per patient, with approximately [REDACTED]% of these patients having undergone reinduction therapy with ipilimumab. The annual percentage increases in utilisation after the first year would be calculated as described in the submission (see table after paragraph 6.65 above). Any annual pembrolizumab expenditure beyond these caps should be rebated [REDACTED]% to the Commonwealth to generate the reduced effective price to apply from initial listing until such time as it might change at the end of the MES.
- The review of new evidence should be provided as soon as possible (and expected to be within two years) after maximal follow-up of the KN-006 trial, noting that the final analysis of OS for this trial is expected to report in the second quarter of 2016.
- The clinical evaluation for KN-006 should formally report both PFS (using RECIST 1.1 and irRC) and OS using the standard graphics of Kaplan-Meier curves, and with standard reporting of results (log rank p-values, hazard ratios with 95% confidence intervals, medians, difference in medians, etc.).
- The economic evaluation based on KN-006 should directly use the Kaplan-Meier curves observed based on individual patient data from the trial to estimate incremental PFS and incremental OS up to the median duration of follow-up across the two arms compared in the clinical evaluation, and then apply extrapolation modelling for both arms for PFS and OS curves from this time point, i.e. no statistical adjustments should be used to account for differential use of post-progression therapies.
- The PBAC considered the following aspects of the model also needed to be applied for the economic evaluation based on data from the completed KN-006 trial.
  - The time horizon of the model to remain at 5 years.
  - The best fit extrapolated curves for both PFS and OS beyond the overall median duration of follow-up of the trial to be structured to converge at 5 years (rather than either 10 years or 40 years).
  - The effective price of ipilimumab to be used.
  - The dispensed price for maximum quantity of pembrolizumab to be back-calculated to result in the proposed ICER of \$45,000/QALY - \$75,000/QALY as per the base case in the pre-PBAC response (corresponding to \$45,000/QALY - \$75,000/QALY on p7, but using dispensed prices).
  - The dose to be 2 mg/kg Q3W, or the price reduced accordingly if the recommended dose or administration frequency has been revised upwards for any reason.

- The mean duration of pembrolizumab therapy in the model to reflect the mean PFS in the model based on the observed data with best-fit extrapolation.
  - The utilities for the progression free health state and the progressed health state in the base case to be justified and fully examined in sensitivity analyses, noting the proposal in the pre-PBAC response to rely on EQ-5D data from KN-006, but without any details of how complete these data would be, nor how they would be used to generate utilities for the model's progression-free and post-progression health states.
  - Adverse event profiles to be based on those reported in KN-006, with costing of adverse events to avoid the potential for double-counting when being adjusted for the cost of providing associated healthcare resources relevant to Australia.
- 6.83 The PBAC foreshadowed that, in the event that this model resulted in revising the pembrolizumab price, the Committee would consider retaining a risk-share arrangement with caps reflecting the duration of pembrolizumab therapy as determined by the trial-based duration of progression-free survival. This is because the PBAC was concerned that progression-defining events would not be assessed as rigorously or as frequently in routine clinical practice as they were in KN-006. The PBAC also noted that, irrespective of the wording of the PBS restriction, pembrolizumab may be continued in the setting of disease progression.
- 6.84 The PBAC noted that the listing of pembrolizumab before the completion of data collection for ipilimumab would reduce confidence in these data for ipilimumab. Similarly, the PBAC noted that there are currently many ongoing trials in malignant melanoma examining different doses and different durations of therapy, and different combinations and different sequences of medicines, and so considered it possible that any MES for pembrolizumab may be similarly affected by likely future changes in clinical practice.
- 6.85 Consistent with its previous managed entry scheme considerations, the PBAC advised that:
- the MES arrangements for pembrolizumab would need to be formalised in the Deed of Agreement established for the purposes of PBS listing
  - the nature of these arrangements should be made public, particularly to inform affected patients, prescribers and competing sponsors
  - any other unexpected but relevant developments emerging before its consideration of the completed KN-006 trial data and associated modelling, such as unexpected safety signals, would be considered according to usual PBAC processes.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended an Authority required listing of pembrolizumab, for the monotherapy treatment of patients with unresectable stage III or metastatic (stage IV) malignant melanoma, with an initial risk share arrangement to achieve the same cost

per patient to the PBS as is currently the case for ipilimumab, to thus give a reduced effective price of pembrolizumab.

- 7.2 The PBAC recommended that PBS listing should be limited to patients who have not been exposed to ipilimumab, noting that in a proposal received after the pre-PBAC response, the sponsor has undertaken to subsidise ongoing access to pembrolizumab for patients who are refractory to ipilimumab. The PBAC recommended that this undertaking should apply to all Australian patients who become refractory to ipilimumab at any time in the future, and should remain in place for as long as pembrolizumab is needed for these patients. Failure to extend the sponsor's undertaking in this way would inequitably create a group of patients who would neither be eligible for PBS subsidy (ipilimumab-naïve only), nor have access to pembrolizumab through other means. The PBAC also noted that patients in the sponsor's existing compassionate use program would have to be accommodated in these new arrangements (depending on whether or not they are refractory to ipilimumab). The PBAC noted that consumer comments indicated there was a high clinical need for pembrolizumab in patients who are refractory to ipilimumab. The PBAC also noted that the medicine is proposed for registration in Australia for use in this group of patients.
- 7.3 The PBAC supported the sponsor's request (affirmed at the hearing) that, for patients with a BRAF mutation, PBS listing of pembrolizumab should follow progression with appropriate dabrafenib therapy (combined with trametinib after trametinib is listed). This is because a comparison across the available trials suggests greater response rates and prolonged median progression-free survival for these cheaper targeted therapies over the immune therapies. The PBAC was informed at the hearing that ongoing trials are comparing different sequence options and that this positioning will be reviewed once these trials are completed.
- 7.4 The PBAC recalled that, in November 2014, it had noted the clinical need and importance of early access to new medicines for melanoma patients and so recommended listing via a managed entry scheme (MES). The PBAC was satisfied that based on early data on some endpoints, pembrolizumab appears more effective than ipilimumab. However the size of the incremental treatment effect is still uncertain, particularly for OS. This uncertainty is the reason for the MES.
- 7.5 In making its recommendation, the PBAC considered that data from the clinical trials presented was reassuring. However, the extent of benefit and costs of pembrolizumab therapy modelled from the comparison of results of selected subgroups from the KN-001 trial of pembrolizumab with the Hodi 2010 published trial of ipilimumab were not convincingly shown to align with the more rigorous early results from the randomised KN-006 trial directly comparing these two therapies in ipilimumab-naïve patients. The sponsor has provided reassurances that more robust evidence will be forthcoming in the foreseeable future to better inform its modelling, and the PBAC has proposed a plan to review this evidence within two years, to make sure patients receiving medicines on the PBS are being treated according to the best available evidence and that the cost of pembrolizumab can be justified in terms of acceptable cost-effectiveness. Should the modelled extent of benefits not be realised, the Committee has recommended measures to minimise risk of unjustified health care expenditure.

- 7.6 The submission's nominated comparator of ipilimumab was considered to be appropriate, especially given that the request to also list pembrolizumab for ipilimumab-refractory patients had been withdrawn in the PSCR and this had been affirmed in the pre-PBAC response.
- 7.7 The PBAC were concerned that the different pembrolizumab dosing regimens used across trials created difficulties in interpreting the results of these studies (especially as side effects and outcomes differed between studies). This uncertainty placed the regulator and the PBAC in a very difficult position as the sponsor was unable to provide a robust explanation for the selection of a dose of 2 mg/kg Q3W, other than it was the lowest (and cheapest) dose regimen. The PBAC noted that variations in regimens applied both to the injected amount (eg 2 mg/kg and 10 mg/kg) and the frequency of injection (eg Q2W and Q3W). The PBAC noted that the pre-PBAC response highlighted the median PFS result from the largest randomised dose comparison in ipilimumab-refractory patients from KN-002 as the primary basis for concluding that there is no variation in dose response across 2 mg/kg Q3W and 10 mg/kg Q3W. The PBAC was concerned that this was a selectively narrow use of all the available evidence and was from a population that had been specifically excluded from the requested listing. On the other hand, the PBAC was also concerned not to over-emphasise the wider sources of evidence that included non-randomised comparisons which were confounded by differences in outcome definitions and durations of follow-up. On balance, the PBAC agreed with the TGA delegate's approach to assessing all randomised comparisons across different dosage regimens as the most rigorous basis for assessing dose response, and concluded that, overall, this randomised evidence suggested (but certainly did not guarantee) that there were no important differences in effectiveness or safety across the compared dosage regimens. This was important for two reasons. First, because this indicates that additional expenditure cannot be justified for pembrolizumab doses or frequencies greater than 2 mg/kg Q3W, so that if a greater dose is subsequently shown to be necessary, then the price of pembrolizumab should be reduced so that the cost per patient remains the same. Second, because the KN-006 trial, which is to be used as the basis for the MES, randomised pembrolizumab patients to 10 mg/kg Q2W or Q3W rather than to 2 mg/kg Q3W.
- 7.8 The PBAC considered that the claim of superior comparative effectiveness of pembrolizumab over ipilimumab was probably reasonable, but noted that the extent of incremental effectiveness and duration of benefit could not be estimated with confidence given the limitations of the current evidence base.
- 7.9 The PBAC noted that, in comparison with cytotoxic therapy, there are new challenges associated with assessing and valuing response and progression following immune inhibitors. As has previously been noted, the proposed value of immune inhibitors relates to possibility of long-term remission or even cure in a subgroup of patients.
- 7.10 The PBAC noted that the TGA had not completed its review of this medicine and that the relevant clinical data had been revealed to the Committee incrementally throughout the process of evaluation well after the lodgement of the initial submission. This meant that the data on which the PBAC was basing its recommendation had not undergone the usual evaluation process. The PBAC

considered it was important to emphasise that the rigorous process of evaluation is designed to protect patients and prescribers and that subverting this process carries risks for patients and the Commonwealth. The PBAC was also concerned that being required to accept the KN-006 data as being confidential created problems with respect to the full disclosure of these potential risks.

- 7.11 The PBAC considered that the most rigorous comparative data for the ipilimumab-naïve population came from the early results of KN-006, which superseded the original submission's non-randomised comparison of selected KN-001 cohorts receiving pembrolizumab with the Hodi 2010 cohort receiving ipilimumab, and also the pre-PBAC response's attempt to match the KN-001 cohorts with the Hodi 2010 cohort as an adjustment of this comparison.
- 7.12 The PBAC considered that the statistically significant increase in overall response rates (from 12% with ipilimumab to 33% with pembrolizumab) and the statistically significant prolongation in median progression-free survival based on the RECIST criteria (from 2.8 months with ipilimumab to 4.1 months with pembrolizumab) were likely to be clinically meaningful. Changing the definition and assessor of progression events increased the difference in median progression-free survival (from 3.3 months with ipilimumab to 7.2 months with pembrolizumab). However, the PBAC noted that overall response rates for pembrolizumab were substantially less than the 90% response rate which was strongly reported by consumers who met with PBAC representatives prior to the meeting. The PBAC was unable to determine how the discrepancy between the consumers' perception and the measured benefit had arisen. The PBAC noted that there might be some responder bias in these perceptions (those who experienced or were aware of instances of poor outcomes would be less likely to advocate for the medicine), and that the selected results of subgroups of KN-001 published in two peer-reviewed journal articles (Robert et al, 2014 and Hamid et al, 2013) had conveyed a more favourable impression of pembrolizumab than the data submitted from KN-001 or KN-006 as the basis for the PBAC consideration. The PBAC noted again that early results of studies are often very favourable and that over time the true impact of a medicine is revealed to be less impressive.
- 7.13 The PBAC considered that the overall survival data were immature, consistent with the monitoring committee of the trial, which did not recommend that the trial be stopped following the interim analysis. Median overall survival had not been reached. Consistent with its observations from other trials, the PBAC expected that the hazard ratio would tend towards the null with additional follow-up, and so the interim estimate with its 95% CI is likely to be biased in favour of pembrolizumab.
- 7.14 The PBAC concluded that pembrolizumab is no worse than ipilimumab in terms of safety, and possibly less toxic. The Committee noted that the time profile of the development of adverse effects of immune-related therapies can be delayed, including to beyond the cessation of treatment, which needed to be considered in this comparative assessment. Available evidence indicated that severe adverse events with ipilimumab do not necessarily recur when exposed to medicines of the pembrolizumab class, so anti-PD1 antibodies can be safely used in patients pre-exposed to ipilimumab. However, given that the requested listing is for ipilimumab-

naïve patients, the PBAC noted that there was no corresponding evidence presented about the safety of ipilimumab after pembrolizumab.

- 7.15 The PBAC further noted the submission emphasised that the perceptions of the safety profile of ipilimumab had deteriorated since PBAC had recommended its listing in November 2012. For example, the need to use steroids or other biological immunosuppressant medicines to manage the underlying colitis frequently associated with ipilimumab has been emphasised. Despite this, the PBAC noted that there were no statistically significant differences in adverse events between pembrolizumab and ipilimumab in the interim report of KN-006 in ipilimumab-naïve patients. The exception to this was “sponsor-defined events of clinical interest”, which showed significantly fewer adverse events with pembrolizumab 10 mg/kg Q3W compared to ipilimumab.
- 7.16 The PBAC noted that two versions of the model were provided, the first as part of the major submission lodged in November 2014 (called the original model) and the second with the PSCR on 28 January 2015 (called the revised model). The model provided with the pre-PBAC response on 4 March 2015 was the same as the revised model, with additional sensitivity analyses included. In the revised model, convergence of overall survival was shortened to 10 years from the 40 years used in the original model. In both the original and the revised model, the analysis of costs and benefits was truncated at 5 years.
- 7.17 The PBAC noted that the original and revised models were both based on non-comparative data from selected subgroups of the Phase I KN-001 trial of pembrolizumab and the Hodi 2010 published trial of ipilimumab. Neither model used data from the Phase III randomised trial directly comparing pembrolizumab and ipilimumab (KN-006).
- 7.18 The PBAC considered that the 3-health state structure of the model as transitions from a progression-free health state to a progressed disease health state and to death using different transitions for ipilimumab and pembrolizumab was reasonable. However, the PBAC considered that the model could not be relied upon to estimate the incremental cost-effectiveness of pembrolizumab with sufficient confidence to determine the basis for any price advantage over ipilimumab. The PBAC noted the following concerns with the model, all of which favoured pembrolizumab.
- The model did not use the effective price of ipilimumab, which was not known to the sponsor.
  - It used the requested ex-manufacturer price of pembrolizumab, not the associated dispensed price (the PBAC relied on ICERs generated from the model using the dispensed price).
  - The model’s complete replacement of observed data with fitted curves rather than observed data presented as Kaplan-Meier curves followed by fitted curves for extrapolation reduced confidence in the model and appeared to slow the ability of the sponsor to use new or updated trial data.
  - Its structure for the revised base case in the PSCR and the pre-PBAC response set the convergence of the extrapolated PFS curves to 5 years, but and set the extrapolated OS curves to 10 years before truncating these curves at 5 years, together with truncating the estimates of costs at 5 years (the PBAC was

reassured that neither version of the model presented by the sponsor adopted a time horizon longer than 5 years). The PBAC noted that, although the convergence of the extrapolated OS curves to 40 years set in the original model favoured pembrolizumab to a greater extent, the revised approach maintained an inconsistency across PFS and OS extrapolations and still favoured pembrolizumab. Favourable ICERs from the 5-year truncated results were sensitive to this structure of setting convergence over 10 to 40 years before truncation. Setting convergence of OS to end at 5 years, which would be consistent with the submission's justification of a 5-year model, produced an ICER of \$45,000/QALY - \$75,000/QALY compared to the revised model's base case of \$45,000/QALY - \$75,000/QALY (using the dispensed price for pembrolizumab).

- The model was not varied to reflect the preliminary KN-006 trial data, which appeared to reflect earlier convergence for both PFS and OS than modelled from the comparison of KN-001 subgroups with Hodi 2010, which would be expected to become more pronounced with longer follow-up data. The duration of the projected superiority was not supported by the Kaplan-Meier plots of PFS and OS from KN-006, which show convergence of PFS may occur as early as 12-14 months; or well short of the 5-year convergence of PFS and 10-40 year convergence of OS in the extrapolations of both models.
- The model used utilities derived from Dickson 2011 rather than Beusterien 2009. This favoured pembrolizumab mainly because Dickson 2011 assigned a higher utility to the health state for disease progression. As pembrolizumab patients were predicted to have greater OS, they spent longer in this state.
- The model's base case assumed zero costs of using ipilimumab following pembrolizumab, which was inconsistent with the submission's proposed clinical management algorithm, and its upper sensitivity analysis only examined the costs of 20% patients using ipilimumab after pembrolizumab, whereas the PBAC expected that pembrolizumab would largely displace rather than replace ipilimumab. The revised model's sensitivity analysis reflected the fact that some KN-001 participants received such therapy and their OS contributed to the estimated OS across all KN-001 participants contributing to the model.
- The model assumed that pembrolizumab treatment ceased at disease progression. Given that this would not occur for all patients, the model underestimated pembrolizumab treatment costs. The PBAC noted that one option would be to vary the model to allow for continued treatment for a proportion of patients, which would be likely to occur in clinical practice. However, the PBAC considered that this would introduce greater uncertainty due to the need to also vary the corresponding stream of post-progression health outcomes. The PBAC therefore preferred to address this uncertainty by modifying the proposed RSA to rebate the cost of any use of pembrolizumab following progression (see paragraph 6.82 above), because no evidence was provided to justify such use in terms of cost-effectiveness.
- The costs of adverse events appeared to be double-counted because they were counted in the INTUITION study of ipilimumab as part of disease management costs, as well as being counted independently as additional costs based on adverse events reported in the trials.

- 7.19 In the light of the above, the PBAC was of the view that the MES proposal should be modified and that consideration be given to a Deed of Agreement with a risk-share component and a managed entry scheme component. The PBAC therefore proposed re-specifications of this model in a future evaluation, when the final data from the KN-006 are available to inform a revised model.
- 7.20 The PBAC accepted the following assumptions regarding the economic model and estimates, noting that, with the exception of the last assumption, they all favoured pembrolizumab:
- not increasing the background rate of all-cause mortality to account for the population getting older during the model
  - costs of disease management for both ipilimumab and pembrolizumab being based on Australian patients receiving ipilimumab in the INTUITION study
  - adverse effects being limited to the rates reported in ipilimumab-naïve patients.
- 7.21 The PBAC advised that these assumptions would not be reopened in any reconsideration of pembrolizumab because of their relatively small consequences for the evaluations once the Committee's advice about converging the PFS and OS extrapolation curves at 5 years is implemented.
- 7.22 The PBAC considered that the annual numbers of patients projected from an epidemiological basis to receive pembrolizumab were overestimated. The PBAC observed that the uptake of ipilimumab had already stabilised at about 800 patients per year and considered that there was no basis to consider that substantially more patients would receive pembrolizumab than would receive ipilimumab. Similarly, the projected cost offsets for ipilimumab are also substantially overestimated compared to existing annual ipilimumab expenditure of about \$86 million, even before the rebate to achieve the effective price is factored in to the estimates. The PBAC also considered that pembrolizumab would displace ipilimumab rather than replace it, and so considered that the estimate of 12% of patients starting ipilimumab after pembrolizumab from KN-001 was an underestimate.
- 7.23 The PBAC recommended that pembrolizumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.24 The PBAC advised that pembrolizumab is not suitable for prescribing by nurse practitioners.
- 7.25 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.26 The PBAC noted that this submission is not eligible for an Independent Review.

**Outcome:**

Recommended

**8 Recommended listing**

Public Summary Document – March 2015 PBAC Meeting

8.1 Add new items:

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB Initial treatment Powder for injection, 50 mg	240 mg	5	\$ [REDACTED] (public) \$ [REDACTED] (private)	Keytruda® MK

Treatment phase: Initial – BRAF V600 mutation negative	
Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Treatment must be the sole PBS-subsidised therapy for this condition;  AND  The patient must be negative for a BRAF V600 mutation;  AND  The condition must be previously untreated;  AND  The treatment must not exceed a total of 6 doses at a maximum dose of 2mg/kg every 3 weeks.
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	Note: 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.  No increase in the maximum number of repeats may be authorised.

Treatment phase: Initial – BRAF V600 mutation positive	
Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Unresectable Stage III or Stage IV

Public Summary Document – March 2015 PBAC Meeting

<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Treatment must be the sole PBS-subsidised therapy for this condition;</p> <p>AND</p> <p>The patient must be positive for a BRAF V600 mutation;</p> <p>AND</p> <p>The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) unless contraindicated or not tolerated according to the TGA approved Product Information;</p> <p>AND</p> <p>The condition must be previously untreated with ipilimumab;</p> <p>AND</p> <p>The treatment must not exceed a total of 6 doses at a maximum dose of 2 mg/kg every 3 weeks.</p>
<b>Prescriber Instructions</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
<b>Administrative Advice</b>	<p>Note: 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.</p> <p>No increase in the maximum number of repeats may be authorised.</p>

<b>Treatment phase: Grandfathered continuing</b>	
<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>	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>	Continuing

Public Summary Document – March 2015 PBAC Meeting

<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The treatment must be the sole PBS-subsidised therapy for this condition;</p> <p>AND</p> <p>The treatment must be for continuing therapy in a patient who commenced treatment with pembrolizumab prior to [listing date];</p> <p>AND</p> <p>Patient must have stable or responding disease;</p> <p>AND</p> <p>The treatment must not exceed a maximum dose of 2 mg/kg every 3 weeks.</p>
<b>Administrative Advice</b>	No increase in the maximum number of repeats may be authorised.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB <b>Continuing treatment</b> Powder for injection, 50 mg	240 mg	7	\$ [REDACTED] (public) \$ [REDACTED] (private)	Keytruda® MK

<b>Treatment phase: Continuing</b>	
<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>	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>	Continuing
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

<b>Clinical criteria:</b>	Treatment must be the sole PBS-subsidised therapy for this condition;  AND  Patient must have previously been issued with an authority prescription for this drug for this condition;  AND  Patient must have stable or responding disease;  AND  The treatment must not exceed a maximum dose of 2 mg/kg every 3 weeks.
<b>Administrative Advice</b>	No increase in the maximum number of repeats may be authorised.

## 9 Context for Decision

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

## 10 Sponsor's Comment

MSD is pleased that the PBAC made the decision to recommend pembrolizumab for patients who have unresectable or metastatic melanoma, and will be working with the Department to ensure that these patients have PBS reimbursed access as soon as possible.