

## 6.06 PEMBROLIZUMAB

### 50 mg injection: powder for, 1 vial, Keytruda<sup>®</sup>, Merck Sharp & Dohme (Australia) Pty Ltd.

#### 1 Purpose of Application

- 1.1 Pembrolizumab has a 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.
- 1.2 The submission was lodged to fulfil the requirements of the Managed Entry Scheme (MES) under which it was PBS-listed and to seek PBAC reconsideration of the cost-effectiveness of pembrolizumab.

#### 2 Requested listing

- 2.1 The submission did not seek any changes in the restriction, which is summarised below.

Name, Restriction, Manner of administration and form	Max. Amount	№. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
<b>PEMBROLIZUMAB</b>				
<b>Initial treatment</b>				
Powder for injection, 50 mg	240 mg	5	\$ [REDACTED] (public)	Keytruda <sup>®</sup> MK
<b>Continuing treatment</b>				
Powder for injection, 50 mg	240 mg	7	\$ [REDACTED] (private) \$ [REDACTED] (effective)	

<b>Treatment phase: Initial</b>	
Severity	Unresectable Stage III or Stage IV
Condition	Malignant melanoma
Clinical criteria	<p><b>BRAF V600 mutation negative</b></p> <p>Treatment must be the sole PBS-subsidised therapy for this condition AND 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 2 mg/kg every 3 weeks.</p>
Clinical criteria	<p><b>BRAF V600 mutation positive</b></p> <p>Treatment must be the sole PBS-subsidised therapy for this condition AND The condition must be positive for a BRAF V600 mutation AND Patient must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor); OR treatment with a BRAF inhibitor is contraindicated or not tolerated according to the TGA approved Product Information AND The condition must be previously untreated with ipilimumab AND</p>

	The treatment must not exceed a total of 6 doses at a maximum dose of 2 mg/kg every 3 weeks.
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.
<b>Treatment phase: Continuing</b>	
Severity	Unresectable Stage III or Stage IV
Condition	Malignant melanoma
Clinical criteria	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 AND Patient must have stable or responding disease AND The treatment must not exceed a maximum dose of 2 mg/kg every 3 weeks.
Administrative advice	No increase in the maximum number of repeats may be authorised.

- 2.2 The requested effective price of pembrolizumab was altered during the evaluation to reflect changes to the way chemotherapy preparation fees are paid under the Section 100 Efficient Funding of Chemotherapy (EFC) arrangement under the 6th Community Pharmacy Agreement (CPA) which took effect on 1 July 2015.
- 2.3 As the majority of chemotherapy preparations are compounded in settings where a \$102.67 preparation fee applies, this fee was applied to calculation of the DPMA in the submission. Using the updated preparation fee, the pembrolizumab DPMA cost per vial required to meet the \$45,000/QALY - \$75,000/QALY ICER increased by a dollar to \$██████████. The ex-manufacturer price needed to produce this cost decreased by almost four dollars (to \$██████████) from the original requested AEMP of \$██████████. These revised costs were also applied to the model and in Section E.

### 3 Background

- 3.1 Pembrolizumab was registered by the TGA on 16 April 2015 as monotherapy for the treatment of unresectable or metastatic melanoma in adults.
- 3.2 Pembrolizumab was previously considered by the PBAC in March 2015 and received a positive recommendation for monotherapy treatment of unresectable or metastatic melanoma.
- 3.3 The March 2015 submission was made in the context of an MES on the basis of a cost-utility analysis compared to ipilimumab. The basis of evidence in the original submission were 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).
- 3.4 Following the February 2015 ESC meeting, early results from a randomised open-label trial comparing pembrolizumab and ipilimumab (KN-006) were made available. These results formed the main basis of the clinical evidence leading to the positive recommendation made by the PBAC. The PBAC concluded that pembrolizumab is no worse than ipilimumab in terms of safety, and possibly less toxic (paragraph 7.14,

March 2015 PSD). The PBAC also 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 (paragraph 7.8, March 2015 PSD).

- 3.5 While the PBAC considered the general 3-health state structure of the model to be reasonable, the PBAC also considered that the model could not be relied upon to estimate the incremental cost-effectiveness of pembrolizumab (paragraph 7.18, March 2015 PSD). The PBAC pointed out a number of concerns with the model, and the key concerns were reflected in the Deed of Agreement.
- 3.6 The Deed of Agreement dated August 2015 had a number of obligations for the sponsor, including lodging a further submission based on the KN-006 trial. The table below provides a summary of the clauses in Attachment B.2 of the Deed, listing the company's obligations and the responses contained in the current submission.

**Table 1: Summary of obligations in the Deed of Agreement, August 2015**

<b>Summary of obligations in B.2.2</b>	<b>Comment on submission response</b>
<u>B.2.2.a</u> : Directly use Kaplan-Meier curves from KN-006 up to median follow-up to estimate incremental PFS and incremental OS.	Complied with the Deed of Agreement and was performed in Section C.7 of the submission.
<u>B.2.2.b</u> Apply extrapolation modelling for both arms of the model for PFS and OS with no statistical adjustment to account for use of post-progression therapies.	Complied with the Deed of Agreement and was performed in Section C.7 of the submission.
<u>B.2.2.c</u> Use a time horizon of 5 years as per the original model.	<i>Did not comply with the Deed of Agreement.</i> The submission maintained that a time horizon of 10 years is appropriate for OS, and had only limited the time horizon to convergence of extrapolated PFS at 5 years
<u>B.2.2.d</u> Use best fit extrapolated curves for both PFS and OS beyond the median duration of follow-up which are to be structured to converge at 5 years.	<i>Did not comply with the Deed of Agreement.</i> The submission maintained that a time horizon of 10 years is appropriate for OS, and had only limited the time horizon for PFS. Long-term mortality information from Schadendorf 2015 was used in lieu of fitted curves for ipilimumab with a hazard ratio applied to estimate pembrolizumab OS.
<u>B.2.2.e</u> Use the effective price of ipilimumab as monotherapy as comparator.	Complied with the Deed of Agreement and was performed in Section D.4 of the submission.
<u>B.2.2.f</u> Back-calculate the DPMQ and/or effective DPMQ to generate an ICER of \$45,000 – \$75,000//QALY as per the original model.	Complied with the Deed of Agreement and was performed in Section D.4 of the submission.
<u>B.2.2.g</u> Use the drug dose of 2 mg/kg Q3W or reduce the price of the drug accordingly.	Complied with the Deed of Agreement and was performed in Section D.4 of the submission.
<u>B.2.2.h</u> Include the mean duration of therapy in the model, which should reflect the mean duration of PFS.	Complied with the Deed of Agreement and appeared in Excel file “Pembrolizumab Section D Workbook November 2015” (refer “Results” worksheet) accompanying the submission.
<u>B.2.2.i</u> Include justified and fully examined utilities for the PFS health state, and the progressed health state of the model.	Complied with the Deed of Agreement and was performed in Section C.6 of the submission.
<u>B.2.2.j</u> Include AE event profiles to be based upon those reported in the final outcomes of KN-006.	Complied with the Deed of Agreement. The AEs included in the model were derived from KN-006, although there was only a statistically significant difference between the two treatments for the AE of colitis.

AE=adverse event; OS=overall survival; PFS=progression-free survival  
Source: Compiled during the evaluation.

- 3.7 The PBAC noted the non-compliance by the sponsor with sections B.2.2.c and B.2.2.d.
- 3.8 Although not required as part of the Deed of Agreement, the submission made a number of additional requests around post-MES conditions of listing for pembrolizumab. These requests were as follows:
- An increase in the number of patients initiated on treatment, including an adjustment to year 1 to account for patients accrued prior to PBS listing.
  - Agreement on an effective dispensed price per vial of \$ [REDACTED] and effective AEMP price per vial of \$ [REDACTED]. This price was based on the modelled economic evaluation, as under the Deed of Agreement, the sponsor was to back-calculate the DPMQ to result in an ICER of \$45,000/QALY - \$75,000/QALY. It was also revised during the evaluation to account for the use of the \$102.67 preparation fee.
  - Drug costs attributed to patients in the year of treatment, ie aligned to the PFS curve.
  - Consequential changes to the budget caps in the Deed of Agreement. The submission specified an update of the caps from year 2 onward to reflect payment for prevalent patients remaining on therapy beyond their first year of treatment.
  - The existing Deed structure and gross list AEMP of \$ [REDACTED] to be maintained.
- 3.9 The above requests by the sponsor were considered in light of the positive recommendation made by the November 2015 PBAC meeting for nivolumab, on a cost-minimisation basis with pembrolizumab. While information regarding the PBAC recommendation was not available prior to the lodging of the current submission, should nivolumab be listed on the PBS, then consideration of the outcomes of the current submission, and the requests within it, would be affected.

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

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

- 4.1 The PBS restriction for pembrolizumab for the treatment of unresectable or metastatic melanoma places its use as follows:
- first-line for patients who are BRAF mutation negative (BRAF wild type);
  - second-line, following progression on a BRAF/MEK inhibitor, for patients who are BRAF mutation positive.
- 4.2 The submission did not discuss potential alterations in the clinical management algorithm, for example the possibility that the requirement under current PBS restrictions that patients with a BRAF mutation must use a BRAF/MEK inhibitor as first-line therapy may be removed and PD-1 inhibitors will be able to be used as first-line therapy in patients with BRAF mutations. Given the rapidly changing landscape of melanoma treatment, consideration of these possibilities would have been informative, particularly in regard to potential uptake of pembrolizumab.

## 5 Comparator

- 5.1 Ipilimumab was the main comparator, as it was in the March 2015 submission. With the recent PBAC recommendation of nivolumab (which occurred after the submission was lodged), nivolumab would also be a relevant comparator.

*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 presented an overview of the key trial, including the reasons for stopping it early; presented further arguments for an increase in the risk share arrangements (RSA) cap based on a higher than expected "bolus" of grandfathered patients; and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing did not add substantively to the evidence presented in the submission.

### **Consumer comments**

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

### **Clinical trials**

- 6.3 The submission was based on KN-006 (N=834), the randomised, open-label trial comparing pembrolizumab and ipilimumab for which early results were presented just prior to the March 2015 PBAC meeting.
- 6.4 Publication details of KN-006 are provided in the table below, and the key features of the trial are in the table following.

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

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
KN-006	CSR P006V02 <sup>a</sup> : A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma.	MSD August 2015
	Robert C, Schachter J, Long GV et al. Pembrolizumab versus ipilimumab in advanced melanoma.	NEJM 2015; 372: 2521-32

<sup>a</sup> While Table B.2-3 of the submission identified the CSR as P006V01 the actual CSR provided with the submission was labelled P006V02.

Source: Table B.2-3, p43 of the submission.

**Table 3: Summary of KN-006**

Trial ID	N	Treatment arms	Trial design	Primary outcome	Use in the economic evaluation
KN-006	834	Pembrolizumab 10 mg/kg Q2W n=279	Phase III R, OL, MC	OS; PFS	PFS+OS; utilities; AEs
		Pembrolizumab 10 mg/kg Q3W n=277			
		Ipilimumab 3 mg/kg Q3W n=278			

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.2-4, p43-44 of the submission.

- 6.5 While this trial was a head-to-head comparison of pembrolizumab and ipilimumab, it used a 10 mg/kg dose of pembrolizumab, administered every 2 weeks (Q2W) or every 3 weeks (Q3W), which differs from the 2 mg/kg Q3W dose registered for use in Australia.
- 6.6 The submission stated that both the TGA and the PBAC have accepted the equivalence of 2 mg/kg and the 10 mg/kg based on the data from the KN-001 trial. As the PBAC noted in paragraph 7.7 of the March 2015 PSD, the evidence available at the time of the TGA assessment did rule out the possibility of important differences in efficacy or safety across the dosage regimens. Nothing was provided in the current submission to alleviate the possibility there may be differences in survival and safety for the 10 mg/kg dose compared to the 2 mg/kg dose. Information on the efficacy and safety of the 2 mg/kg dose may become available with completion of a number of on-going trials. ESC noted that the Pre-Sub-Committee Response (PSCR) sought to counter this claim by drawing attention to the MES which implicitly accepted the dosing in KN-006 as appropriate to decision-making.
- 6.7 The results presented in the current submission were based on the second interim analysis of KN-006 based on the 3 March 2015 data cut. Review of this analysis by the External Data Monitoring Committee (eDMC) found that the trial had met its two primary endpoints by demonstrating a statistically significant and clinically meaningful improvement in OS and PFS. It was recommended that the trial be stopped early and patients who had been treated with ipilimumab be allowed to access pembrolizumab. The eDMC also recommended that patients continue to be followed for OS until the planned final analysis, which is scheduled to be performed after 435 OS events have occurred or after all patients have at least 21 months of follow-up, whichever occurs first. ESC noted that this key clinical trial was stopped early for efficacy considerations, before the OS data could be considered to be mature, and that further OS data collection was continuing.
- 6.8 PBAC had advised that the clinical (and economic) evaluations should be based on the standard ITT analysis given the risk of contamination due to patients receiving post-trial pembrolizumab or switching to other therapies (paragraph 6.79 of the March 2015 PSD), with no statistical adjustments to be used to account for differential use of post-progression therapies (clause B.2.2.b of the Deed of Agreement). The submission did not provide any discussion of the planned use of the Rank Preserving Structural Failure Time (RPSFT) model to account for cross-over in KN-006 for the planned final analysis. Patients treated with ipilimumab with progressive disease were able to access pembrolizumab once the trial was stopped. The clinical study report (CSR) indicated that the RPSFT methodology would be used at the final analysis of this further data collection, ie after 435 deaths or 21

months. The CSR stated that not all of the supportive or exploratory analyses such as RPSFT were performed and reported at the time of the current CSR for the second interim analysis before cross-over was permitted, so it was assumed for the purposes of the evaluation that such methodology was not applied to the analyses presented in the submission.

***Comparative effectiveness***

- 6.9 Survival results from the second interim analysis of KN-006, based on the 3 March 2015 data cut are provided in the table below, followed by the Kaplan-Meier curves for OS and PFS.

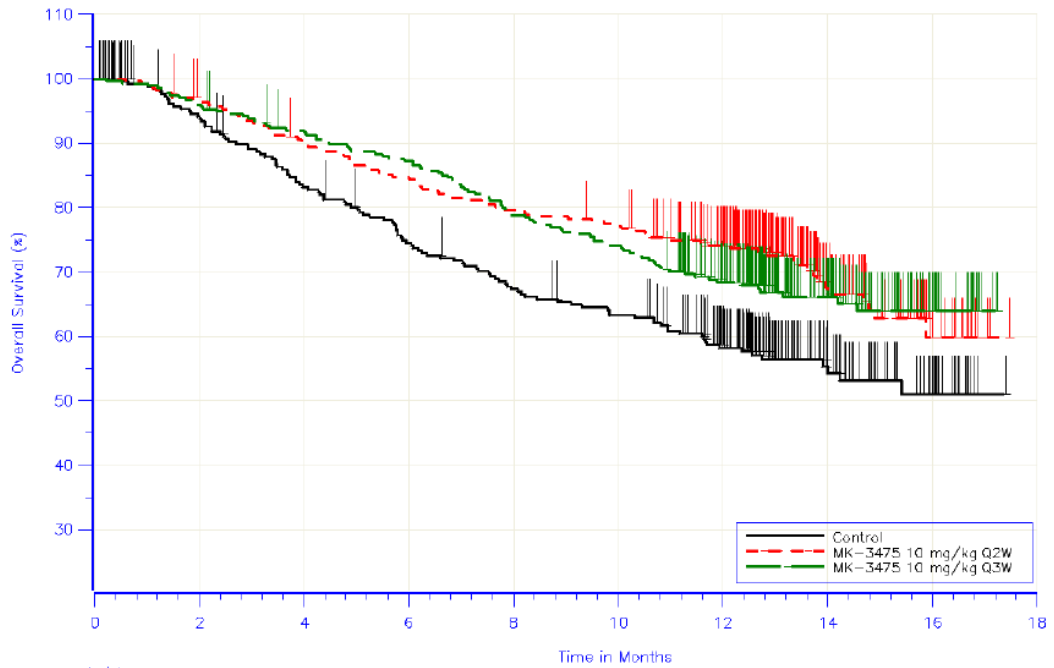
Table 4: OS and PFS results in KN-006

Outcome	Pembrolizumab			Ipilimumab	Absolute difference	HR (95% CI) vs. ipilimumab
	10 mg/kg Q2W N=279	10 mg/kg Q3W N=277	Combined N=556	3 mg/kg Q3W N=278		
<b>Overall survival</b>						
Median follow-up	13.8 months				-	-
Died	85 (30.5%)	92 (33.2%)	177 (31.8%)	112 (40.3%)	Q2W: -9.8% Q3W: -7.1% Comb'd: -8.5%	-
Median OS, mths (95% CI)	NR (., .)	NR (., .)	NR (., .)	NR (12.7, .)	-	Q2W: 0.63 (0.47,0.83) Q3W: 0.69 (0.52,0.90) Comb'd: 0.65 (0.52, 0.83)
OS rate at 12 mths (95% CI)	74.1% (68.5, 78.9)	68.4% (62.5, 73.5)	71.3% (67.2, 74.9)	58.2% (51.8, 64.0)	Q2W: 15.9% Q3W: 10.2% Comb'd: 13.1%	-
<b>Progression-free survival - RECIST 1.1</b>						
Median follow-up	13.8 months				-	-
Progressed	173 (62.0%)	170 (61.4%)	343 (61.7%)	198 (71.2%)	Q2W: -9.2% Q3W: -9.8% Comb'd: -9.5%	-
Median PFS, mths (95% CI)	5.5 (3.4, 7.4)	4.1 (2.9, 7.2)	4.8 (3.7, 6.5)	2.8 (2.8, 2.9)	Q2W: 2.7 Q3W: 1.3 Comb'd: 2.0	Q2W: 0.60 (0.49,0.74) Q3W: 0.59 (0.48,0.73) Comb'd: 0.60 (0.50, 0.72)
PFS rate at 12 mths (95% CI)	37.7% (31.7, 43.7)	36.3% (30.3, 42.3)	37.0% (32.7, 41.2)	17.2% (12.4, 22.5)	Q2W: 20.5% Q3W: 19.1% Comb'd: 19.8%	-
<b>Progression-free survival – irRC</b>						
Number of events	158 (56.6%)	153 (55.2%)	311 (55.9%)	194 (69.8%)	Q2W: -13.2% Q3W: -14.6% Comb'd: -13.9%	-
Median PFS, mths (95% CI)	8.4 (5.6, 12.3)	8.4 (5.7, 12.0)	8.4 (6.6, 11.2)	3.3 (2.9, 4.2)	Q2W: 5.1 Q3W: 5.1 Comb'd: 5.1	Q2W: 0.53 (0.43, 0.66) Q3W: 0.53 (0.43, 0.66) Comb'd: 0.53(0.44, 0.64)
PFS rate at 12 mths (95% CI)	44.8% (38.6, 50.7)	43.0% (36.9, 49.1)	43.9% (39.5, 48.1)	19.5% (14.5, 24.9)	Q2W: -25.3% Q3W: -23.5% Comb'd: -24.4%	-

Comb'd=combined 10 mg/kg Q2W and 10 mg/kg Q3W; HR=hazard ratio; irRC=immune-related response criteria; mths=months; NR=not reached; OS=overall survival; PFS=progression-free survival

Source: Table B.6-1, p60; B.6-5, p68 of the submission and Table 11-1, p203; Table 11-2, p205; Table 11-3, p207; Table 11-4, p209; Table 11-5, p211 Table 11-6, p213; Table 11-9, p225; Table 11-10, p227 of the KN-006 CSR.

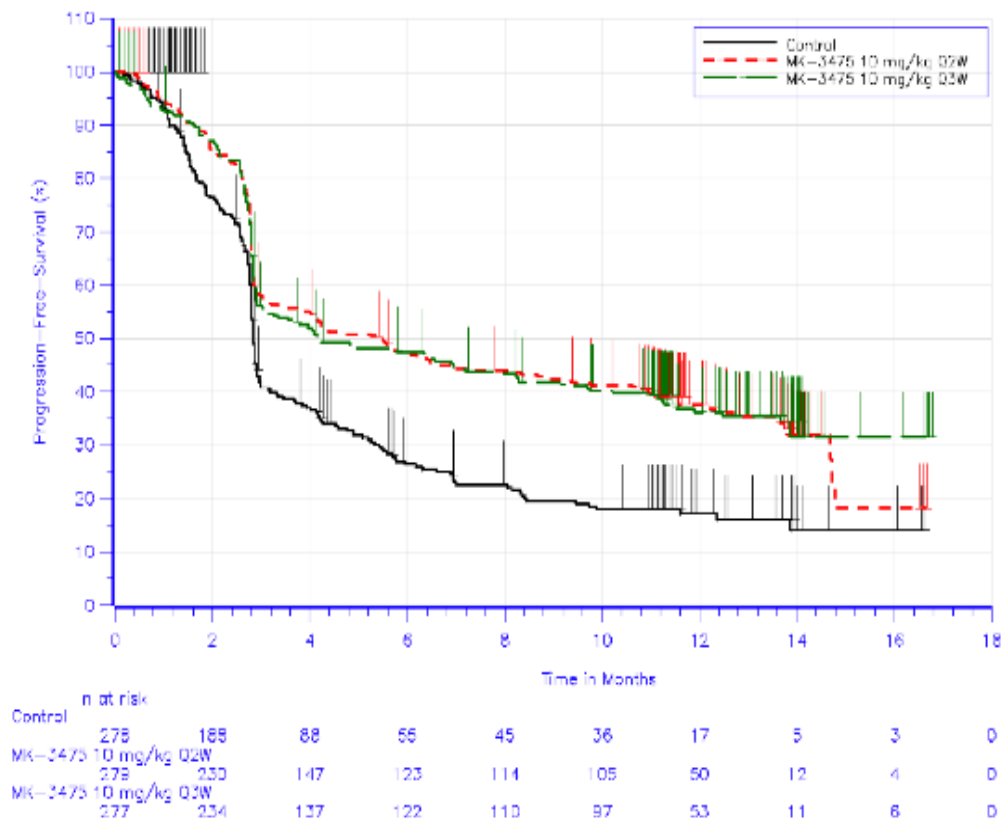
Figure 1: Kaplan-Meier curves of overall survival - KN-006



	n	at risk								
Control	278	242	212	188	169	157	117	51	17	0
MK-3475 10 mg/kg Q2W	279	256	248	233	219	212	177	67	19	0
MK-3475 10 mg/kg Q3W	277	266	251	238	215	202	158	71	18	0

Source: Figure B.6-1, p63 of the submission.

Figure 2: Kaplan-Meier curves of progression-free survival - KN-006



Source: Figure B.6-3, p67 of the submission.

- 6.10 Median overall survival had not been reached in any of the treatment groups at the time of analysis. The statistical comparisons indicated significantly greater OS with both doses and the combined doses of pembrolizumab compared to ipilimumab. While not displayed in the table above, there were no statistically significant differences between the two doses of pembrolizumab for OS.
- 6.11 Progression-free survival results showed an absolute difference compared to ipilimumab of 2 months for the combined doses, 2.7 months for 10 mg/kg Q2W and 1.3 months for the 10 mg/kg Q3W dose. The hazard ratios indicated a statistically significant advantage over ipilimumab for both doses and the combined dose of pembrolizumab. Results based on investigator assessment using irRC also found significant advantages for pembrolizumab, along with greater median months of PFS (5.1 months for both pembrolizumab doses) than the primary results based on RECIST 1.1.
- 6.12 Results were very similar to those presented in February 2015 based on the September 2014 data cut – absolute differences in median months of PFS were the same across groups (2.7 months for pembrolizumab Q2W and 1.3 months for Q3W) and median OS was not reached. The point estimates for the hazard ratios did change slightly, but all comparisons showed a statistically significant advantage for pembrolizumab.

- 6.13 The table below provides results for the quality of life scales used in KN-006, EORTC-QLQ-C30 and EQ-5D.

**Table 5: EORTC-QLQ-C30 and EQ-5D results in KN-006**

	N	Baseline mean (SD)	N	Week 12 mean (SD)	N	Change from baseline LS mean (95% CI)
<b>EORTC-QLQ-C30</b>						
Ipi 3 mg/kg Q3W	211	67.3 (24.0)	148	64.5 (25.6)	131	-9.9 (-13.01, -6.72)
Pembro 10 mg/kg Q2W	239	71.4 (20.4)	172	71.1 (19.3)	159	-2.3 (-5.21, 0.62)
Pembro 10 mg/kg Q3W	228	70.9 (21.6)	187	69.5 (22.4)	168	-2.6 (-5.44, 0.23)
<b>Pairwise comparison - EORTC-QLQ-C30</b>						<b>Difference in LS means (95% CI)</b>
Pembro 10 mg/kg Q2W vs. Q3W						-0.03 (-4.26, 3.63)
Pembro 10 mg/kg Q2W vs. Ipi 3 mg/kg Q3W						7.6 (3.40, 11.75)
Pembro 10 mg/kg Q3W vs. Ipi 3 mg/kg Q3W						7.3 (3.15, 11.38)
<b>EQ-5D</b>						
Ipi 3 mg/kg Q3W	190	0.77 (0.22)	143	0.72 (0.24)	128	-0.10 (-0.13, -0.07)
Pembro 10 mg/kg Q2W	233	0.80 (0.19)	169	0.80 (0.20)	156	-0.01 (-0.04, 0.01)
Pembro 10 mg/kg Q3W	219	0.78 (0.19)	183	0.78 (0.21)	165	-0.02 (-0.04, 0.01)
<b>Pairwise comparison - EQ-5D</b>						<b>Difference in LS means (95% CI)</b>
Pembro 10 mg/kg Q2W vs. Q3W						-0.00 (-0.04, 0.04)
Pembro 10 mg/kg Q2W vs. Ipi 3 mg/kg Q3W						0.08 (0.04, 0.13)
Pembro 10 mg/kg Q3W vs. Ipi 3 mg/kg Q3W						0.08 (0.04, 0.12)

Source: Table B.6-11, p79 and Table B.6-12, p82 of the submission.

- 6.14 Both scales showed statistically significantly greater change from baseline in quality of life for pembrolizumab compared to ipilimumab. However, these differences did not reach the pre-specified MCID criteria of 10 points difference in mean change from baseline. It is unknown what proportion of subjects in each group achieved a 10-point or greater change from baseline to Week 12. The EQ-5D results were transformed using Australian weights and were applied in the modelled analysis.

### **Comparative harms**

- 6.15 A summary of adverse events (AEs) in KN-006 is provided in the Table 6.

Table 6: Summary of Tier 1 and Tier 2 adverse events in KN-006

Adverse event	Pembrolizumab		Ipi 3 mg/kg Q3W N=256	Difference (95%)	
	10 mg/kg Q2W N=278	10 mg/kg Q3W N=277		Pembro Q2W vs. ipi	Pembro Q3W vs. ipi
<b>Tier 1 events</b>					
Sponsor defined events of interest	62 (22.3%)	78 (28.2%)	48 (18.8%)	4.7 (-3.4, 13.1)	9.7 (0.7, 18.2)
Grade ≥3 diarrhoea <sup>a</sup>	8 (2.9%)	3 (1.1%)	9 (3.5%)	-1.3 (-5.4, 2.0)	-0.3 (-6.0, 4.3)
Grade ≥3 colitis <sup>a</sup>	4 (1.4%)	7 (2.5%)	18 (7.0%)	<b>-5.4 (-11.1, -1.3)</b>	<b>-5.0 (-10.6, -1.0)</b>
Grade ≥2 pneumonitis <sup>a</sup>	1 (0.4%)	7 (2.5%)	1 (0.4%)	-0.2 (-3.3, 2.6)	<b>3.6 (0.2, 8.1)</b>
Grade ≥3 hypo- or hyperthyroidism <sup>a</sup>	0 (0%)	0 (0%)	1 (0.4%)	-0.3 (-3.5, 2.3)	-0.3 (-3.5, 2.2)
Grade ≥3 skin toxicity <sup>a</sup>	1 (0.4%)	4 (1.4%)	3 (1.2%)	-0.6 (-4.1, 2.1)	-0.0 (-3.2, 3.0)
Immune-related AE	127 (45.7%)	117 (42.2%)	111 (43.4%)	1.0 (-10.2, 11.5)	-1.8 (-12.9, 8.6)
<b>Tier 2 events</b>					
Serious drug-related events	34 (12.2%)	26 (9.4%)	45 (17.6%)	<b>-7.8 (-15.6, -0.9)</b>	-7.4 (-16.0, 0.6)
Discontinued - drug-related event	15 (5.4%)	22 (7.9%)	24 (9.4%)	-4.3 (-11.0, 1.1)	-2.7 (-9.3, 3.2)
Any drug-related grade 3-5 event	42 (15.1%)	35 (12.6%)	51 (19.9%)	<b>-7.1 (-15.3, -0.1)</b>	-4.2 (-13.5, 4.5)

<sup>a</sup> with potential immunologic aetiology

Source: Table B.6-15, p86 and Table B.6-17, p87-88 of the submission.

- 6.16 The analyses showed statistically significantly fewer patients treated with pembrolizumab experienced grade ≥3 colitis, while significantly fewer patients treated with ipilimumab experienced grade ≥2 pneumonitis compared to those treated with pembrolizumab 10 mg/kg Q3W. Significantly fewer patients treated with pembrolizumab 10 mg/kg Q2W experienced serious drug-related AEs or any drug-related grade 3-5 AEs compared to those treated with ipilimumab. This difference may have limited relevance given the Q2W frequency of dosing is not used in Australia.
- 6.17 The modelled evaluation included the following AEs, all of which were grade ≥3 events with potential immunologic aetiology (with the exception of thyroid disorders, which were of any grade): endocrine disorders; colitis; diarrhoea; asthenia/fatigue; infections and infestations; hypertension and thyroid disorders. Of the AEs included in the model there were only statistically significant differences between pembrolizumab and ipilimumab for colitis, favouring pembrolizumab.

### **Benefits/harms**

- 6.18 A summary of the comparative benefits and harms for pembrolizumab versus ipilimumab is presented in the Table 7.

Table 7: Summary of benefits and harms for pembrolizumab and ipilimumab based on the second interim analysis of KN-006

Benefits					
	Pembro10 mg/kg Q2W + Q3W combined N=556	Ipi 3 mg/kg Q3W N=278	Absolute difference	HR (95% CI)	
<b>Overall survival</b>					
Died	177 (31.8%)	112 (40.3%)	-8.5%	-	
Median mths (95% CI)	NR (., .)	NR (12.7, .)	-	0.65 (0.52, 0.83)	
OS rate at 12 months	71.3% (67.2, 74.9)	58.2% (51.8, 64.0)	13.1%	-	
<b>Progression-free survival - RECIST 1.1</b>					
Progressed	343 (61.7%)	198 (71.2%)	-9.5%	-	
Median mths (95% CI)	4.8 (3.7, 6.5)	2.8 (2.8, 2.9)	2.0 months	0.60 (0.50, 0.72)	
PFS rate at 12 mths (%)	37.0% (32.7, 41.2)	17.2% (12.4, 22.5)	19.8%	-	
<b>Progression-free survival – irRC</b>					
Progressed	311 (55.9%)	194 (69.8%)	-13.9%	-	
Median mths (95% CI)	8.4 (6.6, 11.2)	3.3 (2.9, 4.2)	5.1 months	0.53 (0.44, 0.64)	
PFS rate at 12 mths (%)	43.9% (39.5, 48.1)	19.5% (14.5, 24.9)	24.4%	-	
<b>Harms</b>					
	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 colitis <sup>b</sup>	4 (1.4%)	7 (2.5%)	18 (7.0%)	-5.4 (-11.1, -1.3)	-5.0 (-10.6, -1.0)
Grade ≥2 pneumonitis <sup>b</sup>	1 (0.4%)	7 (2.5%)	1 (0.4%)	-0.2 (-3.3, 2.6)	3.6 (0.2, 8.1)
Sponsor-defined events of clinical interest	62 (22.3%)	78 (28.2%)	48 (18.8%)	4.7 (-3.4, 13.1)	9.7 (0.7, 18.2)

<sup>a</sup> Based on Miettinen & Nurminen method stratified by line of therapy, PD-L1 status and ECOG

<sup>b</sup> with potential immunologic aetiology

Comb'd=combined; diff=difference; HR=hazard ratio; ipi=ipilimumab; irRC=immune-related response criteria; mths=months; NR=not reached; OS=overall survival; PFS=progression-free survival; pembro=pembrolizumab; Q2W=every 2 weeks; Q3W=every 3 weeks

Source: Table B.6-1, p60; B.6-5, p68 of the submission and Table 11-1, p203; Table 11-2, p205; Table 11-3, p207; Table 11-4, p209; Table 11-5, p211 Table 11-6, p213; Table 11-9, p225; Table 11-10, p227 of the KN-006 CSR.

- 6.19 On the basis of the KN-006 data with a median follow-up of 13.8 months, for every 100 patients treated with pembrolizumab compared with ipilimumab:
- 13 more patients will be alive at 13.8 months
  - 20 more patients will not have progressed at 13.8 months
  - 5 fewer patients will have experienced grade ≥3 colitis
  - 4 more patients will have experienced grade ≥2 pneumonitis

### Clinical claim

- 6.20 The submission described pembrolizumab as superior in terms of comparative effectiveness and superior in terms of comparative safety over ipilimumab.
- 6.21 The claim for superior safety is not strongly supported. The submission argued that while the frequency of drug-related adverse events of special interest (AEOSIs) was

higher with pembrolizumab than ipilimumab, the frequency of high-grade AEOSIs, serious AEOSIs and AEOSIs leading to discontinuation was approximately 2-fold greater for ipilimumab-treated patients compared to those treated with pembrolizumab. The submission added that this suggests any AEOSIs due to pembrolizumab were milder and more easily managed. This claim was not entirely accurate, as not all AEOSIs associated with pembrolizumab were milder. In addition, while the analyses presented by the submission showed statistically significantly fewer patients treated with pembrolizumab experienced grade  $\geq 3$  colitis, there were also significantly fewer patients treated with ipilimumab who experienced grade  $\geq 2$  pneumonitis compared to those treated with pembrolizumab 10 mg/kg Q3W. While there were significantly fewer patients treated with pembrolizumab 10 mg/kg Q2W who experienced serious drug-related AEs or any drug-related grade 3-5 AEs compared to those treated with ipilimumab, this difference had limited relevance given the Q2W dosing frequency is not used in Australia. Overall, with the exception of colitis, there was little indication of statistically superior safety for pembrolizumab compared to ipilimumab.

- 6.22 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.23 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

### **Economic analysis**

- 6.24 The submission presented a cost-utility analysis based on KN-006, as required under the Deed of Agreement. The table below provides a summary of the model structure.

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

<b>Component</b>	<b>Summary</b>
Time horizon	10 years in the base case versus 13.8 months median follow-up in KN-006
Outcomes	QALYs
Methods used to generate results	Partitioned survival analysis: PFS: Kaplan-Meier curves to 13.8 months followed by fitted parametric functions to 5 years from baseline. OS: for ipilimumab, Kaplan-Meier curve to 13.8 months followed by long-term ipilimumab data reported by Schadendorf 2015. For pembrolizumab, Kaplan-Meier curve to 13.8 months followed by application of accelerated failure time model for hazard function applied to ipilimumab OS.
Health states	Progression-free survival (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)	OS and PFS weekly distributions from Kaplan-Meier curves to 13.8 months and thereafter from extrapolated curves to 5 years for PFS and 10 years for OS.

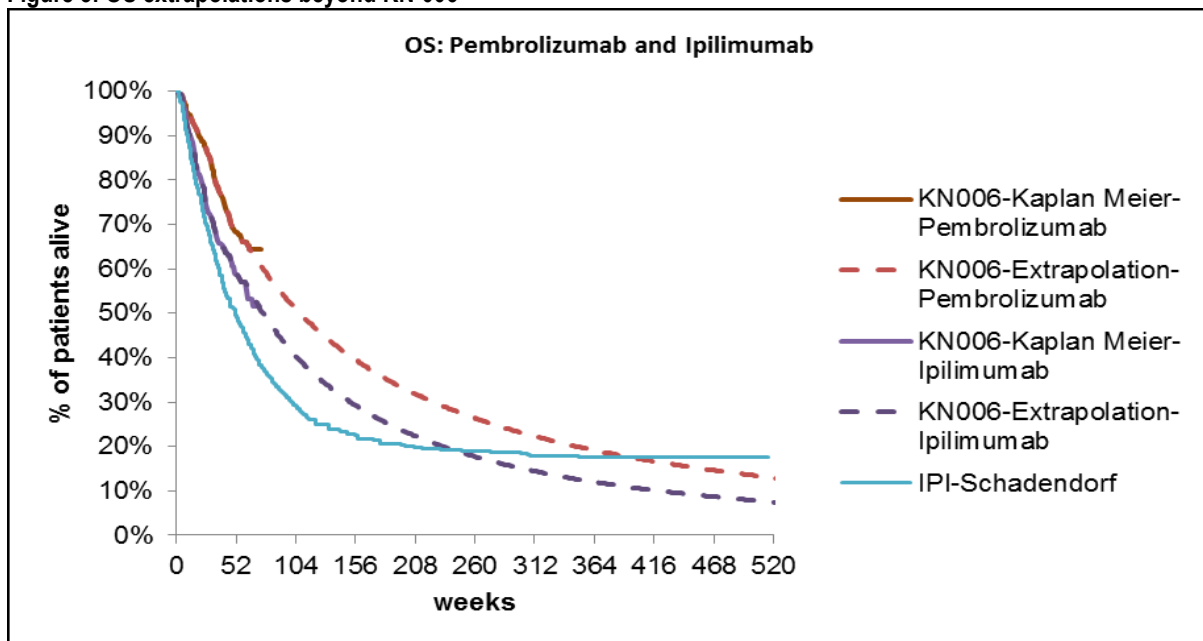
Source: Compiled during the evaluation.

- 6.25 The model complied with most clauses of the Deed of Agreement, including the requirement to use Kaplan-Meier curves to median duration of follow-up and then apply extrapolation. The exceptions were time horizon of 5 years and the requirement for extrapolated PFS and OS to both converge at 5 years. The

submission argued that, because the earliest convergence of the PFS curves occurred at 5.2 years, it was not plausible for both PFS and OS to converge at 5 years, as required under clause B.2.2.d of the Deed. The PBAC considered that this extrapolation was not strongly evidence-based, because it depended on the assumptions built into the modelled extrapolation beyond the observed PFS results from the KN-006 trial up to 13.8 months mean duration of follow-up across the trial population.

- 6.26 On the basis that extrapolation of ipilimumab data from KN-006 did not adequately capture the long-term “plateauing” effect for OS associated with ipilimumab, the submission instead used results from Schadendorf 2015 (maximum follow-up of 119 months) to extrapolate OS from 13.8 months to 10 years for ipilimumab (see Figure 3). The submission applied an accelerated failure time model hazard ratio based on the log-normal distribution of long-term ipilimumab OS data (Schadendorf 2015) to generate the OS extrapolation for pembrolizumab beyond the Kaplan-Meier curve (this curve is not plotted in Figure 3: it would have a similar “plateaued” shape as the IPI-Schadendorf curve, but would lie above the IPI-Schadendorf curve).

Figure 3: OS extrapolations beyond KN-006



Source: Figure D.6-2, p. 193 of the submission.

- 6.27 ESC considered that the methods used by the submission to extrapolate OS resulted in implausible outcomes. While it may be reasonable to expect a “plateau” for both ipilimumab and pembrolizumab, the use of ipilimumab data from Schadendorf 2015 to generate the OS extrapolation for pembrolizumab did not reflect actual pembrolizumab data. Given available evidence, assuming the “plateau” for pembrolizumab would occur at a higher level than ipilimumab could not be supported as the reasons for the “plateau” were not yet known. It was yet to be shown whether the “plateau” was a disease effect (in which case pembrolizumab would serve merely to slow the progression towards this “plateau”), or whether specific products can modify outcomes for OS.

- 6.28 Most importantly, the results generated by the model were unrealistic, as incremental life-year gains accrued in the post-progression health state (0.53) were greater than gains in the PFS health state (0.37), and, while convergence of extrapolated PFS occurred at 5 years, the effect in terms of OS was maintained indefinitely thereafter (see results below).
- 6.29 The PBAC considered that level at which any “plateau” might occur in the long-term overall survival of melanoma patients treated “off-trial” with immune therapies remained uncertain. In relation to this, the PBAC noted the publication in *Oncology Letters* 2016 Feb; 11(2): 1581-5 of long-term survival in metastatic melanoma patients treated with ipilimumab where “the 1- and 2-year overall survival rates were 42% and 13%, respectively, whilst survival for ≥3 years was observed in 8.6% of patients”. The PBAC considered that these real world efficacy data provide less support than the Schadendorf 2015 results for the level of any “plateau” effect from treatment with ipilimumab and consequently the more favourable “plateau” effect claimed for pembrolizumab. The PBAC noted that the differences between these results may reflect whether the study occurred in the context of a clinical trial (Schadendorf 2015) or in the real world setting.
- 6.30 Key drivers of the model are identified in the table below.

**Table 9: Key drivers of the model**

Description	Method/Value	Impact
Estimate of OS	Extrapolation of OS for pembrolizumab and ipilimumab used ipilimumab-based data (Schadendorf 2015) after the trial period.	High, favours pembrolizumab
The relationship between PFS and OS	The submission assumed OS for pembrolizumab would “plateau” at a higher level than ipilimumab.	High, favours pembrolizumab
Utility values	KN-006 EQ-5D results were transformed using Australian weights.	Moderate, higher utility values for post PD favour pembrolizumab

OS=overall survival; Post-PD=progressive disease  
Source: Compiled during the evaluation.

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

**Table 10: Results of the economic evaluation**

Component	Pembrolizumab	Ipilimumab	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYS	3.86	2.96	0.90
QALY	2.32	1.78	0.55
<b>Incremental cost/extra life-year gained</b>			\$ [REDACTED]
<b>Incremental cost/extra quality-adjusted life-year (QALY) gained</b>			\$ [REDACTED]

Source: Table D.5-8, p190 of the submission.

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

- 6.32 The base case ICER estimated by the model matched the numeric value specified in the Deed of Agreement. However, it was not likely to accurately represent the cost-effectiveness of pembrolizumab. Generation of this ICER relied upon convergence of extrapolated PFS at 5 years and superiority in OS for pembrolizumab-treated patients which continued indefinitely thereafter. In a 10-year model, this overestimated incremental OS.

- 6.33 The model produced the implausible result that the effect upon PFS diminished by 5 years, but the effect in terms of OS was maintained indefinitely thereafter. This did not support the claim, made in the 2015 submission (and not discussed in the current submission), that PFS is a robust predictor of OS (Flaherty 2014).
- 6.34 Some issues remained with the model in relation to the appropriateness of including all-cause mortality and the estimate of disease management costs, but the PBAC resolved in March 2015 that these issues would not be reopened due to their minor impact upon the ICER (paragraph 7.21, March 2015 PSD).
- 6.35 The model was highly sensitive to both the time horizon of the model, and the OS extrapolation function selected for pembrolizumab. The incremental cost/QALY was consistently \$75,000/QALY - \$105,000/QALY in response to changes in the survival parameters. This demonstrated that the base case ICER estimated by the model, while it matched the numeric value specified in the Deed of Agreement, was not likely to accurately represent the cost-effectiveness of pembrolizumab.
- 6.36 The PSCR examined the effect of altering the key modelling assumptions for OS in three analyses along with two supplementary analyses. However the ESC noted that these analyses also: i) substantially increased the probability of colitis in the ipilimumab arm; and, ii) doubled the costs of treating colitis in each of the new analyses. Both of these variations differed from what had previously been agreed under clause B.2.2.j of the Deed. They also both resulted in increasing the back-calculated dispensed price of pembrolizumab in all scenarios. This was not reasonable because the rate of colitis in the pembrolizumab arm of the model was not informed by similar data and may well be higher in routine care (as the PSCR argued for ipilimumab). The PBAC also noted, but did not accept as informative, the further variation of the model which was provided in the Pre-PBAC Response, and so was not independently verified. This model converged the overall survival curves at 7 years, but also retained the imbalance in the sources of data to increase the cost offsets of managing colitis.

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

- 6.37 The cost per patient (revised for use of the updated preparation fee) was based on average vial use ([REDACTED] vials) over [REDACTED] weeks of treatment, determined by PFS in the economic model. The viability of this cost depended on the accuracy of treatment duration as generated by the model.

**Estimated PBS usage & financial implications**

- 6.38 The submission was not considered by DUSC. On the basis of usage data from the sponsor's [REDACTED]-month named patient program, the submission claimed that patient numbers used to determine the current caps, i.e. based on ipilimumab usage, were 'grossly' underestimated. The named patient program recruited [REDACTED] patients, from which the submission calculated an average of 116 patients per month accessing pembrolizumab ([REDACTED]/[REDACTED] months) to suggest that in excess of 1,400 new patients would be treated with pembrolizumab per year. Based on this, the submission argued again that an epidemiological approach is justified, rather than the approach recommended by the PBAC in March 2015.

- 6.39 The submission’s epidemiological approach used extrapolated melanoma mortality data sourced from the AIHW to estimate the eligible population. Clinician-sourced uptake rates were applied. The named patient program was used to estimate a revised number of grandfathered patients. The submission calculated estimated costs for the revised patient numbers, and provided the difference between the revised costs and current cap levels as the net cost to the PBS. A summary of key components of the financial estimates is provided in the table below.
- 6.40 For its estimates, the submission used years 1 to 6, with year 1 being the first 12 months of listing of pembrolizumab under the MES (September 2015 to August 2016); year 2 the first full year of listing under the current submission; with years 2 to 6 representing the first 5 years of listing under the current submission. Estimates are provided below including the MES year, with the following years presented as years 1 to 5.

**Table 11: Estimated patient numbers and cost**

	MES yr	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Eligible patients</b>						
BRAF mutant	█	█	█	█	█	█
BRAF wild type	█	█	█	█	█	█
Total eligible	█	█	█	█	█	█
<b>Uptake</b>						
BRAF mutant	█%	█%	█%	█%	█%	█%
BRAF wild type	█%	█%	█%	█%	█%	█%
<b>Treated patients</b>						
BRAF mutant	█	█	█	█	█	█
BRAF wild type	█	█	█	█	█	█
Grandfathered	█					
<b>Total treated</b>	█	█	█	█	█	█
Current MES cap	█	█	█	█	█	NA
Administrations	NA	█	█	█	█	█
Scripts <sup>a</sup>		█	█	█	█	█
Net cost to PBS/RPBS		\$ █	\$ █	\$ █	\$ █	\$ █
Current cap		\$ █	\$ █	\$ █	\$ █	\$ █
<b>After cap net cost PBS/RPBS</b>		\$ █	\$ █	\$ █	\$ █	\$ █

<sup>a</sup> The submission assumed 3.82 vials per administration.

NA=not applicable; yr=year

Source: Table 13, p208; Table 16, p212; Table 20, p216 of the submission; ‘Cost of drug to the PBS RPBS’ and ‘Net cost to PBS’ worksheets of the ‘Nov 15 Section E’ Excel file provided with the submission.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be more than \$100 million per year.

- 6.41 If the changes to patient numbers requested by the submission were implemented following the MES, the estimated net costs to the PBS/RPBS would be more than

\$100 million over the 5 years of listing. The submission's estimates were not likely to be accurate, for the following reasons:

- The financial estimates relied heavily on the modelled economic evaluation (ie to generate the proportion with PFS and consequent duration of treatment as well as to determine the requested price of pembrolizumab). The economic model had a number of issues (see Economic analysis above) that drew into question its accuracy.
- A different source of determining patient weight and consequent vial use was applied in the financial estimates (weight distribution by gender from the ABS) compared to that used in the model (weight distribution from the named patient program). This created an unnecessary inconsistency, with different patient weights in the two models (████ kg for males and █████ kg for females in the financial estimates compared to █████ kg in the economic model).
- Uptake rates were based on averages sourced from 8 clinicians and were likely to be biased. It was a small sample of clinicians, and the submission provided no information regarding what criteria were used to select the clinicians (outside of the statement the sponsor asked a question of '8 leading melanoma specialists in Australia'); whether conflict of interest was obtained from the clinicians; and what background information was provided to them.
- The mortality extrapolations used by the submission to estimate eligible patients were based on a database that pre-dated the availability of BRAF/MEK inhibitors in Australia. Since pembrolizumab is currently restricted to second-line use in BRAF mutation positive patients, the impact of dabrafenib and trametinib on survival in this patient population was relevant to estimating population size. Consequently, the submission's estimates may not be accurate.
- Adverse event costs, which were included in the modelled evaluation, were not included in the financial estimates. This meant that actual costs were likely to be underestimated. MBS costs were also not included.
- Although the sponsor was unaware of this prior to lodging the submission, given the recent PBAC recommendation of nivolumab on a cost-minimisation basis with pembrolizumab, market share between the two drugs would become relevant should nivolumab be listed on the PBS.

6.42 The Pre-PBAC Response further argued for increasing the patient numbers, noting greater than expected numbers of grandfathered patients, initial experience with ex-wholesaler data, the fact that observed numbers of patients receiving dabrafenib or ipilimumab did not also take into account patients enrolled in clinical trials, and that more patients were likely to be treated with pembrolizumab than ipilimumab. The PBAC was not persuaded by these arguments which were either based on the first few months of listing – reflecting initial experience in the context of a prevalence pool ("pent up demand") rather than the incidence-based approach proposed by the submission, or apparently and implausibly inferring that trials in malignant melanoma would cease with the listing of pembrolizumab. The PBAC was also aware that the patient numbers in the existing RSA had already been increased to account for the claim that more patients were likely to be treated with pembrolizumab than ipilimumab.

6.43 Sensitivity analyses had limited value given the reliance of the financial estimates on results of the economic model (ie PFS to determine treatment duration and cost of pembrolizumab). As would be expected, increasing variables such as patient weight and uptake rates increased estimated net costs. More informative analyses would

require alteration of the current economic model and application of results to the financial estimates, as well as inclusion of variables such as adverse event costs that were excluded by the submission. Such re-structuring could not be completed during the evaluation period.

### Financial Management – Risk Sharing Arrangements

6.44 The submission requested the following changes to Deed, stating that, based on the changes nominated in the submission and consistent with the PBAC’s view that a risk sharing arrangement with caps might be needed to address the risk that pembrolizumab may be continued in the setting of disease progression (paragraph 6.83, March 2015 PSD):

- Deletion of the further submission clause (clause 3.4) as the current submission in the further submission was based on comparative data from KN-006.
- Update of the subsidisation caps from year 2 onward to reflect:
  - The agreed effective pembrolizumab price per vial as per the current submission, rather than being based on the effective ipilimumab price as is currently the case for the MES Deed.
  - Payment for prevalent patients remaining on therapy beyond their first year of treatment. Having more than quadrupled the number of prevalent patients in the current submission, this represented an ongoing increase in net costs for the duration of treatment for these patients.
  - Higher patient numbers to better reflect the true number of Australians with advanced melanoma who will be treated with a PD-1 inhibitor.

6.45 The submission nominated the estimated net costs to the PBS/RPBS in the current submission as the revised subsidisation caps. The current caps and the revised caps are provided in the table below, with differences between the two estimated during the evaluation.

Table 12: Current and revised caps

	MES year	Year 1	Year 2	Year 3	Year 4	Year 5
Current caps	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Revised caps	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	NA
Difference	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	NA

NA=not applicable

Source: Table F.1-1, p239 of the submission.

6.46 The requested increase in the caps was essentially a doubling of the current caps. The issues with the financial estimates and the underlying issues with the modelled evaluation did not support such an increase in the caps.

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

## 7 PBAC Outcome

7.1 The PBAC decided not to recommend to the Minister (under section 101(3)) that the circumstances, under which pembrolizumab is made available as a pharmaceutical benefit, be changed.

- 7.2 The PBAC noted that the submission brought to a close the Managed Entry Scheme (MES) component of the Deed of Agreement between the sponsor and the Commonwealth of Australia for pembrolizumab within the timeframe stipulated by clause 3.4.1 of the Deed.
- 7.3 The PBAC considered that the updated clinical trial results from KN-006 were similar to those provided in preliminary form for its March 2015 consideration, particularly in terms of PFS and OS. The main purpose of the submission was to incorporate the results of this trial in a revised economic evaluation once formally completed.
- 7.4 The PBAC rejected the modelling approach used in the economic evaluation which generated 58% of the incremental life-year gains in the post-progression health state by extending the time horizon to 10 years and assuming an indefinite incremental gain in overall survival beyond 3 years.
- 7.5 The submission argued for the extension of the time horizon beyond the agreed 5 years on the basis that the modelled extrapolation of PFS suggested some patients were still progression-free by year 5. The PBAC considered that this extrapolation was not strongly evidence-based, because it depended on the assumptions built into the modelled extrapolation beyond the observed PFS results from the KN-006 trial up to 13.8 months mean duration of follow-up across the trial population.
- 7.6 More importantly, the PBAC considered that level at which any “plateau” might occur in the long-term overall survival of melanoma patients treated with immune therapies remained uncertain. The PBAC noted that, of the modelled incremental life-years gained of 0.90, 0.37 (42%) were modelled as being in the progression-free health state and 0.53 (58%) were modelled as being in the post-progression health state. In relation to the level of any “plateau”, the PBAC noted a recent publication of ipilimumab treatment in metastatic melanoma in a real world setting showed that the 1- and 2-year overall survival rates were 42% and 13%, respectively, whilst survival for  $\geq 3$  years was observed in 8.6% of patients. Given these circumstances, the causal attribution of any claim for long-term survival in a proportion of patients commencing an immune therapy remains unclear. Protagonists for this type of therapy have attributed prolonged survival in a subset of patients (a “plateau”) to the use of the immune therapy for a less prolonged duration. However, this attribution implicitly relies on non-randomised comparisons with other follow-up data following other management options (including no active intervention, suggesting a long-term historical survival of 10%: Balch et al, *J Clin Oncol* 2001;19:3635-48), which were not formally presented for assessment. As noted previously, the PBAC accepted that immune therapy prolonged survival in a proportion of patients, however the incremental gain in survival and the duration of benefit still remained uncertain. In addition, the PBAC noted that the model produced the implausible result that the effect upon PFS diminished by 5 years, but the effect in terms of OS was maintained indefinitely thereafter. This did not support the claim, made in the 2015 submission (and not discussed in the current submission), that PFS is a robust predictor of OS (Flaherty 2014).
- 7.7 The PBAC noted that no economic evaluation was presented that fully met the agreed outline of the MES as an alternative to the rejected economic evaluation.

- 7.8 The PBAC separately rejected the submission's request for an increase in patient numbers contributing to the risk share arrangements (RSA) noting concerns about the basis for estimating the duration of pembrolizumab treatment, which increased the numbers of patients assumed to receive treatment for more than a year, and the basis for estimating the uptake rates, which were likely to be biased upwards.
- 7.9 The PBAC was not persuaded by further arguments in the Pre-PBAC Response for increasing the patient numbers which were either based on the first few months of listing – reflecting initial experience in the context of a prevalence pool (“pent up demand”) rather than the incidence-based approach proposed by the submission, or apparently and implausibly assuming that trials in malignant melanoma would cease with the listing of pembrolizumab. The PBAC was also aware that the patient numbers in the existing RSA had already been increased to account for the claim that more patients were likely to be treated with pembrolizumab than ipilimumab.
- 7.10 Recalling that it had previously considered that the annual numbers of patients projected from an epidemiological basis were overestimated, the PBAC was not satisfied that the current basis for this aspect of the RSA should be supplanted.
- 7.11 The PBAC also noted that, since the Deed of Agreement, it had recommended nivolumab be listed for the treatment of unresectable Stage III or Stage IV metastatic melanoma, considering that nivolumab is non-inferior to pembrolizumab. Further, “[t]he PBAC recommended that the pricing of nivolumab upon PBS listing be determined only with reference to the initial pricing conditions of the pembrolizumab MES. Any future pricing adjustment that may be sought for pembrolizumab as part of the conditions of the pembrolizumab MES would not apply to nivolumab, thus providing the Commonwealth certainty of the nivolumab pricing. Future applications to prove cost effectiveness of nivolumab over pembrolizumab may be made at any time by the sponsor, if warranted by future clinical trial data. In the unlikely event that the pembrolizumab MES reveals pembrolizumab to be clinically inferior to ipilimumab, then the cost per patient to the PBS for both pembrolizumab and nivolumab monotherapy would need to be reconsidered. The PBAC noted that a rebating arrangement would be needed to achieve the intended pricing outcome. The Committee recommended that the Department negotiate a rebating arrangement with the sponsor in a manner that can be implemented and managed by the Department.” (paragraph 7.6, Nivolumab PSD November 2015 PBAC meeting) The PBAC noted that, in the event that nivolumab is listed on the PBS on the basis of this recommendation, the price and RSA of pembrolizumab would also be linked to the price and RSA of nivolumab, which would remain consistent with the initial pricing and RSA conditions of the pembrolizumab MES.
- 7.12 The PBAC then noted that key aspects of its March 2015 requests relating to the specification of the economic evaluation to be presented at the end of the MES had not been adhered to despite the sponsor's confirmation that it would do so in the subsequent Deed of Agreement. The PBAC stated that it expected that its requests would first be adhered to in full as an initial base case economic evaluation at the end of the MES. Then it may also be appropriate to identify what else might have emerged since the start of the MES, and to present the consequences of these unforeseen circumstances in a revised economic evaluation for PBAC consideration alongside the initially agreed base case. This could be accompanied by arguments in the submission for why the alternative economic evaluation should instead be

relied upon by the PBAC.

- 7.13 Similarly, the PBAC noted that other unforeseen circumstances may also be relevant to its reconsideration, despite not being included in the submission to close the MES. In this case, the listing of nivolumab as monotherapy for melanoma on a cost-minimisation basis against pembrolizumab as listed at the start of the MES was unforeseen in March 2015, but now has relevant consequences for the implementation of any PBAC recommendation about the price of pembrolizumab following the completion of the MES.
- 7.14 However, the PBAC remained concerned that its confidence in the value of the MES framework overall is diminished if any aspect of what is requested and agreed at the outset is not subsequently presented at all. As the MES agreements are formalised in Deeds of Agreement that can also include other components such as Risk Share Arrangements and Special Price Arrangements, the failure to provide what had previously been agreed raised wider concerns about the confidence the Commonwealth can have in the wider Deed of Agreement framework. Accordingly, the PBAC requested that the Department advise on the options (legal and otherwise) which may be explored in the event that any particular aspect of a Deed of Agreement is ignored.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as an Independent Review is not available in response to a request to modify or extend an existing listing.

**Outcome:**

Rejected

**8 Recommended listing**

No change to the existing listing

**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 wishes to clarify the following matters raised in the minutes:

- The submission provided a sensitivity analysis using the 5 year time horizon as required in the Deed (para 3.6 and 3.7)
- MSD disagrees this submission brings to a close the managed entry scheme (MES) component of the Deed of Agreement (para 7.2). This misrepresents the content of the Deed because there are provisions enabling MSD to make

an additional submission. The Deed provides for a process of good faith negotiations before any changes are made to any MES set up by the Deed. It follows that any decision to close the MES would be by the agreement of both parties

- The “unforeseen circumstance” of the listing nivolumab on a cost minimization basis to pembrolizumab (para 7.13) misrepresents the both the 2011 MES policy and the draft 2015 Managed Access Program policy. There is nothing unforeseen about the listing of a second drug and this does not change the incremental benefit (the “QALY gain”) that the first product in the scheme would have over the original comparator

The PBAC has accepted pembrolizumab’s superiority claim over ipilimumab, hence MSD finds the conclusion that the submission did not provide sufficient basis to justify any change in the conditions over ipilimumab difficult to understand. Pembrolizumab has already benefitted hundreds of PBS patients, at a cost to Government that substantially undervalues the product. MSD will lodge a further submission to ensure that pembrolizumab is fairly evaluated and that its incremental value over ipilimumab appropriately recognised.