

5.10 NIVOLUMAB

**concentrate solution for infusion, 10 mg/mL, 1 x 4 mL vial,
concentrate solution for infusion, 10 mg/mL, 1 x 10 mL vial,
Opdivo[®], Bristol Myers Squibb; plus
IPILIMUMAB**

**concentrate solution for infusion, 5 mg/mL, 1 x 40 mL vial,
concentrate solution for infusion, 5 mg/mL, 1 x 10 mL vial,
Yervoy[®], Bristol Myers Squibb**

1 Purpose of Application

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

2 Requested listing

2.1 The requested restrictions for this use of nivolumab and ipilimumab are provided below, including initial and continuing treatment criteria. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough. The submission presented the ex-manufacturer vial prices instead of dispensed prices per maximum amount. These requested prices are presented below instead of dispensed price for maximum amount (DPMA). With the revised Sections D and E provided, the sponsor sought to limit any specific details on pricing due to potential complexities, therefore the proposed ex-manufacturer prices for nivolumab were not presented.

Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	Ex-manufacturer price	Proprietary Name and Manufacturer
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial	120 mg	3	\$ [REDACTED] (published price) <i>TBA</i> (effective price)	Opdivo BQ
nivolumab 100 mg/10 mL injection, 1 x 10 mL vial			\$ [REDACTED] (published price) <i>TBA</i> (effective price)	

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
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV

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Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	<i>Induction (combination) phase</i>
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:	<p><i>Patient must be receiving PBS-subsidised ipilimumab concomitantly for this condition</i></p> <p><i>AND</i></p> <p><i>Patient must not have received prior treatment with ipilimumab,</i></p> <p><i>AND</i></p> <p><i>The treatment must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.</i></p>
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	<p>The recommended dose and schedule is nivolumab 1 mg/kg and ipilimumab 3 mg/kg combined with every 3 weeks (Q3W) administered as an intravenous (IV) infusion for 4 doses.</p> <p>Treatment will continue as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.</p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>Special Pricing Arrangements apply.</i></p>

Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	Ex-manufacturer price	Proprietary Name and Manufacturer
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial	360 mg	3	\$ [REDACTED] (published price) TBA (effective price)	Opdivo BQ
nivolumab 100 mg/10 mL injection, 1 x 10 mL vial			\$ [REDACTED] (published price) TBA (effective price)	

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
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma

Public Summary Document – November 2015 PBAC Meeting

PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	<i>Continuing (single) phase</i>
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:	<p><i>Patient must have previously been issued with an authority prescription for this drug for this condition</i></p> <p>AND</p> <p><i>Patient must have stable or responding disease</i></p> <p>AND</p> <p><i>The treatment must not exceed a maximum dose of 3 mg per kg every 2 weeks.</i></p>
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	<p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>Special Pricing Arrangements apply.</i></p>

Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	Ex-manufacturer price	Proprietary Name and Manufacturer
IPIILIMUMAB				Yervoy BQ
ipilimumab 200 mg/40 mL injection, 1 x 40 mL vial	360 mg	3	\$ [REDACTED] (published price)	
			\$ [REDACTED] (effective price)	
ipilimumab 50 mg/10 mL injection, 1 x 10 mL vial			\$ [REDACTED] (published price)	
			\$ [REDACTED] (effective price)	

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
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	<i>Induction (combination) phase</i>

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:	<p><i>Patient must be receiving PBS-subsidised nivolumab concomitantly for this condition</i></p> <p>AND</p> <p><i>Patient must not have received prior treatment with ipilimumab</i></p> <p>AND</p> <p><i>The treatment must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.</i></p>
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	<p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>Special Pricing Arrangements apply.</i></p>

- 2.2 The requested listing differed from the PBS listing for pembrolizumab, which is restricted to patients who have not been treated with ipilimumab and to *BRAF*-positive patients who have progressed after BRAF inhibitor treatment. The requested listing also included patients eligible for BRAF inhibitors, which is inconsistent with the PBS listing for pembrolizumab and the revisions made by the PBAC to the nivolumab monotherapy requested listing (July 2015 PBAC minutes).
- 2.3 The submission sought listing based on cost-utility analyses compared to ipilimumab monotherapy, nivolumab monotherapy, and pembrolizumab monotherapy, via direct comparisons against ipilimumab and nivolumab and an indirect comparison against pembrolizumab.

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

3 Background

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate's overview was available.
- 3.2 Nivolumab monotherapy was submitted to the TGA in January 2015. The submission stated that subsequently the TGA also agreed to include results of the safety and efficacy of nivolumab plus ipilimumab in its review. Therefore nivolumab plus ipilimumab combination therapy was expected to have the same TGA timeline as nivolumab monotherapy.
- 3.3 This was the first consideration of nivolumab plus ipilimumab combination therapy by the PBAC. A previous submission for nivolumab monotherapy was rejected by the PBAC in July 2015. Another PD-1 inhibitor, pembrolizumab, was recommended by the PBAC in March 2015 and PBS-listed in September 2015.

- 3.4 During the evaluation of the nivolumab plus ipilimumab submission, the sponsor also lodged a minor re-submission of nivolumab monotherapy seeking listing based on a cost-minimisation in comparison to pembrolizumab.

4 Clinical place for the proposed therapy

- 4.1 The submission considered that most patients receiving nivolumab plus ipilimumab would be *BRAF* wild type patients in the first line, or *BRAF* mutant type patients in the second line. However, the requested restriction included all patients with stage III or IV unresectable metastatic melanoma, irrespective of *BRAF* status or treatment line. The submission considered that, given the severity of the disease, no patients who could derive benefit should be excluded from treatment.
- 4.2 Although the submission's emphasis that treatment should not be withheld from patients who could derive benefit was noted, under the requested restriction nivolumab plus ipilimumab combination therapy would likely substitute for BRAF inhibitors in the first line, but no clinical data was presented in the incomplete indirect comparison with dabrafenib ± trametinib. Consequently, both the clinical and economic basis for the listing in this context was not established.

5 Comparator

- 5.1 The submission nominated ipilimumab monotherapy as the main comparator and nivolumab monotherapy, pembrolizumab, and dabrafenib ± trametinib as additional comparators. In its July 2015 meeting, the PBAC considered that pembrolizumab and not ipilimumab was the most appropriate comparator for nivolumab monotherapy (PBAC July 2015 nivolumab minutes, paragraphs 7.1 and 7.3).
- 5.2 The PSCR (p.1) accepted the change in comparator from ipilimumab monotherapy to pembrolizumab monotherapy. The ESC agreed that pembrolizumab monotherapy is the appropriate comparator.
- 5.3 The submission also included a feasibility analysis of a comparison against dabrafenib ± trametinib, and found that no direct comparisons or indirect comparisons could be conducted. While the lack of relevant evidence could not inform such a comparison, the submission's requested listing and estimated financial implications assumed use of nivolumab plus ipilimumab in place of dabrafenib ± trametinib, for which no clinical evidence was provided.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed how the nivolumab and ipilimumab combination would be used in practice and addressed

other matters in response to the Committee's questions.

Consumer hearing

- 6.2 A meeting between Melanoma Patients Australia and the representatives of the PBAC covered the upcoming PBAC consideration of ipilimumab with nivolumab for metastatic melanoma. The following points provide a summary of the discussion:
- There is a need to provide therapeutic options to treat melanoma, and for these options to be available regardless of what prior treatments have been used. The combination of ipilimumab and nivolumab is perceived as suiting patients whose disease is aggressive.
 - The combination of ipilimumab and nivolumab has a serious adverse event (AE) profile. Reporting of AEs has mainly involved diarrhoea, fatigue, skin irritation and rash, however clinicians have become more adept at managing these AEs as experience with the drugs is developed.
 - The possible long-term effects of the drugs used in this combination on pituitary function (e.g. Lam et al. *Ipilimumab-induced hypophysitis in melanoma patients: an Australian case series*. Intern Med J 2015; 45(10):1066-73) and vision were also noted as having been recently identified. It was considered that these effects could be observed with both agents, but are potentially magnified with the combination.
 - The patient view on accepting a higher risk of AEs with the combination of drugs compared with the agents used sequentially – patients would likely opt for the combination only where it is needed to treat more aggressive forms of the disease.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (24), health care professionals (5) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the perceived benefits of treatment with combination nivolumab and ipilimumab, including slowing the progression of disease and the clinical need for effective treatment in patients with high disease burden.
- 6.4 The PBAC noted advice received from the Medical Oncology Group of Australia describing that “nivolumab monotherapy and in combination with ipilimumab and pembrolizumab monotherapy represent the new standards of care for advanced melanoma and offer patients significant survival and quality of life benefits, with manageable side effects in contrast to standard chemotherapy.”

Clinical trials

- 6.5 The submission was based on one head-to-head trial comparing nivolumab plus ipilimumab combination therapy to nivolumab and ipilimumab monotherapies (CA209-067: N=945) and one head to head trial comparing nivolumab plus ipilimumab combination therapy to ipilimumab monotherapy (CA209-069: N=142). The indirect comparison against pembrolizumab, with ipilimumab as the common

reference, used the same two trials as well as KN-006 (N=834) for the pembrolizumab arm.

- 6.6 Details of the trials presented in the submission are provided in Table 1 below with the information for the trials included in the indirect comparison versus pembrolizumab provided in Table 2.

Table 1: Trials (and associated reports) presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
CA-209-067	A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined With Ipilimumab Versus Ipilimumab Monotherapy in Subjects With Previously Untreated Unresectable or Metastatic Melanoma Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma	19 June 2015 <i>NEJM</i> 2015 373 (1) 23-34
CA-209-069	Phase 2, Randomized, Double Blinded, Study of Nivolumab (BMS-936558) in Combination With Ipilimumab vs Ipilimumab Alone in Subjects With Previously Untreated, Unresectable or Metastatic Melanoma Postow MA, Chesney J, Pavlick AC et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma	4 May 2015 <i>NEJM</i> 2015 372 (21) 2006-17

Source: Table 10, p60 of the submission.

- 6.7 Table 2 presents the information for the trials included in the indirect comparison versus pembrolizumab.

Table 2: Trials (and associated reports) presented in the submission

Trial	Description	Reports	Exchangeable?
Common reference: Ipilimumab monotherapy			
Nivolumab plus ipilimumab			
CA209-067	R, DB, MC	as in Table 1 above	No
CA209-069	R, DB, MC	as in Table 1 above	No
Pembrolizumab			
KN-006	R, OL, MC	Robert C, Schachter J, Long GV et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. <i>NEJM</i> 2015 Apr. [Epub ahead of print]	No

Source: Table 66, p175-6 of Sections A and B of the submission.

DB = double blind; MC = multicentre; R = randomised

- 6.8 The main reasons that the trials were not exchangeable were that KN-006 included patients who had already received prior systemic therapies, while the nivolumab plus ipilimumab trials did not; and the baseline characteristics of the trials differed according to mutation status and percent with brain metastases, with the nivolumab plus ipilimumab combination trials having healthier patients.

- 6.9 The key features of the direct randomised trials are summarised in the table below.

Table 3: Summary of trials used in the clinical evaluation

Trial ID	N	Comparison	Trial design	Primary outcome	Use in the economic evaluation
Nivo + Ipi vs Ipi monotherapy					
CA209-067	945	Nivo, 1 mg/kg IV, combined with Ipi 3 mg/kg, Q3W x 4, then Nivo, 3 mg/kg IV Q2W (n =314); Ipi, 3 mg/kg Q3W x 4 (n=315)	Phase III R, DB, MC	PFS, OS*	Pooled PFS HR
CA209-069	142	Nivo, 1 mg/kg IV, combined with Ipi 3 mg/kg Q3W x 4, then Nivo 3 mg/kg IV Q2W (n=95); Ipi 3 mg/kg, Q3W x 4 (n=47)	Phase II R, DB, MC	ORR in BRAF WT patients	
Nivo + Ipi vs. Nivo monotherapy					
CA209-067	945	Nivo, 1mg /kg IV, combined with Ipi 3 mg/kg, Q3W x 4, then Nivo, 3 mg/kg IV Q2W (n =314); Nivo 3 mg/kg IV, Q2W (n=316)	Phase III R, DB, MC	PFS, OS*	PFS HR
Pembro vs Ipi monotherapy					
KN-006	834	Pembro 10 mg/kg Q2W, IV (n=279); Pembro 10 mg/kg Q3W, IV (n= 277); Ipi 3 mg/kg Q3W x 4, IV (n=278)	Phase III R, OL, MC	PFS, OS	PFS HR

Source: compiled during the evaluation.

DB = double blind; HR = hazard ratio; Ipi = ipilimumab; IV = intravenous; MC = multi-centre; Nivo = nivolumab; OL = open label; ORR = objective response rate; OS = overall survival; Pembro = pembrolizumab; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; R = randomised; WT = wild type

*OS data was not made available for this trial.

- 6.10 The submission did not provide any overall survival data for CA209-067 on the basis that the data remained immature, even though overall survival data for the monotherapy arms of the trial were provided in the nivolumab monotherapy Pre-Sub-Committee Response (PSCR) in May 2015. The PSCR (p.1) for the current submission noted that this was based on a local analysis of immature data from CA209-067 and was previously submitted in error. The final OS analysis was anticipated to become available around the third quarter of 2016.

Comparative effectiveness

- 6.11 Table 4 provides a summary of the direct comparison between nivolumab plus ipilimumab combination therapy and ipilimumab monotherapy.

Table 4: Results for PFS and OS from the direct comparison against ipilimumab monotherapy

Trial ID	Nivo + Ipi n/N (%)	Ipi n/N (%)	Absolute difference	HR (95% CI)
Overall survival - CA209-067				
Number of deaths	NR	NR		
Median OS (95% CI), months	NR	NR		NR
Overall survival - CA209-069				
Median follow-up, months	11			
Number of deaths	25/95 (26.3)	17/47 (36.2)		
Median OS (95% CI), months	Not reached	Not reached	-	0.73 (0.39, 1.36)
Progression-free survival - CA209-067				
Median follow-up, months	12.2 to 12.5			
Number of progressions	151/314 (48.1)	234/315 (74.3)		
Median PFS (95% CI), months	11.50 (8.90, 16.72)	2.9 (2.8, 3.4)	8.60	0.43 (0.35, 0.53) Primary analysis: 0.42 (99.5%CI: 0.31, 0.57)
Progression-free survival - CA209-069				
Median follow-up, months	11			
Number of progressions	42/95 (44.2)	32/47 (68.1)		
Median PFS (95% CI), months	Not reached	3.02 (2.76, 5.13)	-	0.39 (0.25, 0.63)
Progression-free survival - pooled analysis				
				0.42 (0.35, 0.51)

Source: Table 26, p99 and Table 23, p93-4 of Sections A and B of the submission.

CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; Nivo + Ipi = nivolumab plus ipilimumab; NR = not reported; OS = overall survival; PFS = progression-free survival

- 6.12 The direct comparison indicated that there was a significant improvement in progression-free survival compared to ipilimumab, but no statistically significant improvement in overall survival. The submission's claim of superiority over ipilimumab monotherapy (see clinical claim below) was focused on progression-free survival.
- 6.13 The submission did not present overall survival data for CA209-067 and stated that overall survival was an exploratory endpoint in CA209-069 and was confounded by post-study therapy.
- 6.14 Although it was difficult for the PBAC to interpret the overall survival results from trial CA209-069 given the issues identified, the PBAC also raised concerns about the submission's focus on progression-free survival results.
- 6.15 Table 5 summarises the efficacy results of the direct comparison against nivolumab monotherapy.

Table 5: Results of PFS from the direct comparison – nivolumab monotherapy

Trial ID	Nivo + Ipi n/N (%)	Nivo n/N (%)	Absolute difference	HR (95% CI)
Progression-free survival - CA209-067				
Number of progressions	151/314 (48.1)	174/316 (55.1)	--	0.74 (0.60, 0.92)
Median PFS (95% CI), months	11.50 (8.90, 16.72)	6.90 (4.34, 9.46)	4.60	--

Source: Table 49, p 150 of Sections A and B of the submission.

CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; Nivo = nivolumab; NR = not reported; OS = overall survival; PFS = progression-free survival

- 6.16 The results indicated a statistically significant improvement in progression-free survival associated with combination therapy compared to nivolumab monotherapy. No overall survival data were presented for this comparison.
- 6.17 Table 6 summarises the efficacy results of the indirect comparison against pembrolizumab.

Table 6: Results of PFS and OS from the indirect comparison against pembrolizumab

Comparison and endpoint	HR (95% CI)
Overall survival - Indirect comparison of Nivo + Ipi (CA-209-069) and Pembro (KN-006)	
Nivo + Ipi vs Pembro Q2W	1.159 (0.398, 3.373)
Nivo + Ipi vs Pembro Q3W	1.058 (0.535, 2.093)
Progression-free survival - Indirect comparison of Nivo + Ipi (pooled*) and Pembro (KN-006)	
Nivo + Ipi vs Pembro Q2W	0.724 (0.54, 0.97)
Nivo + Ipi vs Pembro Q3W	0.724 (0.55, 0.96)

Source: Tables 80 and 81, p228-9 and Tables 84 and 85, p236-7 of Sections A and B of the submission.

CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival; Pembro = pembrolizumab; Q2W = every 2 weeks; Q3W = every three weeks

*Pooled trial data from CA209-067 and CA209-069.

- 6.18 The results of these indirect comparisons indicated that, although there was a statistically significant improvement in progression-free survival for nivolumab plus ipilimumab compared to pembrolizumab, there was no statistically significant improvement in overall survival.

Table 7: Results of objective response rate from the Indirect comparison against pembrolizumab

Comparison and measure	Nivo + Ipi vs. Pembrolizumab Q2W	Nivo + Ipi vs. Pembrolizumab Q3W
Odds ratio (95% CI)	1.89 (0.86, 4.14)	1.96 (0.89, 4.3)
Risk ratio (95% CI)	1.25 (0.66, 2.37)	1.29 (0.68, 2.43)
Risk difference (95% CI)	0.2 (0.09, 0.31)	0.21 (0.1, 0.32)

Source: Tables 88 and 89, p242 and p244 of Sections A and B of the submission.

CI = confidence interval; Nivo + Ipi = nivolumab plus ipilimumab; Q2W = every 2 weeks; Q3W = every 3 weeks

- 6.19 The submission pointed out concerns regarding the indirect comparison. These concerns included the poor exchangeability between the trials, and the difference in dose between KN-006 and the TGA restriction for pembrolizumab.
- 6.20 The poor exchangeability of the trials was a concern. KN-006 included patients who had received previous systemic therapy and KN-006 had less healthy patients than the nivolumab plus ipilimumab trials with respect to percent with brain metastases and mutation status.
- 6.21 Though the PBAC had expressed concerns regarding the different dose in KN-006 and the TGA restriction, it considered that the evidence suggested, but did not guarantee, equivalent efficacy and safety (pembrolizumab PSD March 2015, paragraph 7.7). As the PBAC recommended pembrolizumab despite the dosage inconsistency, and no evidence has been raised in the current submission to challenge this consideration, this dosage issue was not a relevant concern.

Comparative harms

6.22 The submission completed statistical analyses across the two direct comparisons (versus ipilimumab and nivolumab monotherapy) and the indirect comparison versus pembrolizumab. Table 8 provides a summary of the results.

Table 8: Summary of all comparisons – safety outcomes

Adverse event	RD (95% CI)	RR (95% CI)	OR (95% CI)
Pooled CA209-067 and CA209-069: Nivo + Ipi vs Ipi			
Overall drug-related AEs			
Any AE	0.26 (0.20, 0.33)	1.07 (0.97, 1.17)	2.13 (0.67, 6.77)
Any serious AE	0.26 (0.20, 0.33)	2.19 (1.76, 2.74)	3.30 (2.40, 4.55)
Any severe AE (Grade ≥3)	0.28 (0.22, 0.35)	2.05 (1.68, 2.49)	3.34 (2.45, 4.56)
AEs of special interest			
Endocrine	0.21 (0.15, 0.27)	2.64 (1.94, 3.58)	NR
Gastrointestinal	0.07 (0.00, 0.14)	1.15 (1.00, 1.32)	NR
Hepatic	0.23 (0.18, 0.29)	3.20 (2.28, 4.48)	NR
Pulmonary	0.05 (0.02, 0.08)	2.46 (1.24, 4.87)	NR
Drug-related AE leading to discontinuation	0.23 (0.17, 0.29)	2.59 (1.92, 3.49)	3.52 (2.44, 5.08)
CA-209-067 – Nivo + Ipi vs Nivo			
Overall drug-related AEs			
Any AE	0.13 (0.09, 0.18)	1.16 (1.10, 1.23)	4.65 (3.70, 5.85)
Any serious AE	0.40 (0.34, 0.46)	6.00 (4.05, 8.89)	10.6 (6.75, 16.65)
Any severe AE (Grade ≥3)	0.39 (0.32, 0.46)	3.37 (2.57, 4.42)	6.27 (4.42, 8.89)
Drug-related AEs of special interest			
Endocrine	0.16 (0.09, 0.22)	2.09 (1.52, 2.87)	2.56 (1.73, 3.77)
Gastrointestinal	0.27 (0.20, 0.34)	2.38 (1.84, 3.07)	3.57 (2.54, 5.00)
Hepatic	0.18 (0.11, 0.24)	2.38 (1.70, 3.32)	2.97 (1.99, 4.44)
Pulmonary	0.05 (0.02, 0.08)	3.14 (1.36, 7.25)	3.31 (1.39, 7.85)
Drug-related AE leading to discontinuation	0.29 (0.23, 0.35)	4.75 (3.15, 7.17)	6.90 (4.32, 11.01)
Indirect comparison: Nivo + Ipi vs Pembro (via Ipi)			
Adverse event	Nivo+Ipi vs Ipi* RR (95%CI)	Pembro vs Ipi** RR (95%CI)	Nivo+Ipi vs Pembro RR (95%CI)
Overall drug-related AEs			
Any AE	1.07 (0.97, 1.17)	1.04 (0.96, 1.14)	1.03 (0.91, 1.17)
Severe AE (Grade ≥3)	2.07 (1.70, 2.52)	0.59 (0.42, 0.82)	3.51 (2.38, 5.17)
AE leading to discontinuation	2.59 (1.92, 3.49)	0.58 (0.34, 0.97)	4.47 (2.44, 8.16)

Source: compiled during the evaluation.

AE = adverse event; CI = confidence interval; Ipi = ipilimumab; Nivo = nivolumab; NR = not reported; OR = odds ratio; Pembro = pembrolizumab; Q2W = every 2 weeks; Q3W = every 3 weeks; RD = risk difference; RR = risk ratio

*Pooled CA209-067 and CA209-069 data.

**Q2W and Q3W arms of KN-006.

- 6.23 Compared to ipilimumab monotherapy, nivolumab plus ipilimumab had statistically significant higher rates of serious adverse events, severe adverse events (grade 3 or higher), endocrine gastrointestinal, hepatic or pulmonary events, and adverse events leading to discontinuation.
- 6.24 Compared to nivolumab monotherapy, nivolumab plus ipilimumab had statistically significant higher rates of study drug-related adverse events, serious drug-related

adverse events, severe drug-related adverse events and drug-related adverse events leading to discontinuation.

- 6.25 Compared to pembrolizumab, nivolumab plus ipilimumab had statistically significant higher rates of severe adverse events, adverse events leading to discontinuation and drug-related adverse events leading to death. The submission considered that the safety comparison against pembrolizumab should be considered in light of the small numbers of patients being compared.
- 6.26 The analysis showed across all comparisons a worse toxicity profile related to nivolumab plus ipilimumab treatment, particularly in serious and severe adverse events and in adverse events leading to discontinuation.

Benefits/harms

- 6.27 Table 9 presents a summary of the comparative benefits and harms for nivolumab plus ipilimumab versus ipilimumab monotherapy.

Table 9: Summary of comparative benefits and harms for Nivo + Ipi versus Ipi

Benefits						
OS- CA209-069						
	Nivo + Ipi	Ipi	Absolute difference	HR (95% CI)		
Number of deaths n/N (%)	25/95 (26.3)	17/47 (36.2)				
Median OS, months	Not reached	Not reached	-	0.73 (0.39, 1.36)		
PFS- CA209-069						
Number of progressions n/N (%)	42/95 (44.2)	32/47 (68.1)				
Median PFS (95% CI), months	Not reached	3.02 (2.76, 5.13)	-	0.39 (0.25, 0.63)		
PFS- CA209-067						
Number of progressions n/N (%)	151/314 (48.1)	234/315 (74.3)				
Median PFS (95% CI), months	11.50 (8.90, 16.72)	2.9 (2.8, 3.4)	8.60	0.43 (0.35, 0.53)		
Pooled PFS:				0.42 (0.35, 0.51)		
Harms						
	Nivo + Ipi n/N (%)	Ipi n/N (%)	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Nivo + Ipi	Ipi	
Any serious drug-related adverse events						
Pooled**	195/407 (47.9)	78/357 (21.8)	2.19 (1.76, 2.74)	48	22	0.26 (0.20, 0.33)
Any severe adverse events (grade ≥3)						
Pooled**	221/407 (54.3%)	95/357 (26.6%)	2.05 (1.68, 2.49)	54	27	0.28 (0.22, 0.35)
Adverse events leading to discontinuation						
Pooled**	148/407 (36.4%)	50/357 (14.0%)	2.59 (1.92, 3.49)	36	14	0.23 (0.17, 0.29)

Source: compiled during the evaluation.

AE = adverse event; CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival; PFS = progression-free survival; RD = risk difference; RR = risk ratio

* Median follow-up in CA209-067: 12.2-12.5 months; minimum follow-up in CA209-069: 11 months.

**Pooled CA209-067 and CA209-069.

- 6.28 On the basis of the direct comparison presented by the submission, the comparison of nivolumab plus ipilimumab and ipilimumab monotherapy resulted in:
- no statistically significant differences in overall survival
 - a statistically significant difference in PFS, with a median difference of approximately 8.60 months favouring nivolumab plus ipilimumab.

- 6.29 On the basis of the direct comparison presented by the submission, for every 100 patients treated with nivolumab plus ipilimumab compared to ipilimumab monotherapy:
- approximately 26 more patients experienced serious drug-related adverse events
 - approximately 28 more patients experienced severe (grade three or higher) adverse events.
 - approximately 22 more patients experienced adverse events leading to discontinuation of treatment.
- 6.30 Table 10 presents a summary of the comparative benefits and harms for the nivolumab plus ipilimumab versus nivolumab comparison.

Table 10: Summary of comparative benefits and harms for Nivo + Ipi versus Nivo

Benefits						
PFS - CA209-067						
	Nivo + Ipi	Nivo	Absolute difference	HR (95% CI)		
Number of progressions n/N (%)	151/314 (48.1)	174/316 (55.1)	--	0.74 (0.60, 0.92)		
Median PFS (95% CI), months	11.50 (8.90, 16.72)	6.90 (4.34, 9.46)	4.60	--		
Harms						
	Nivo + Ipi n/N (%)	Nivo n/N (%)	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Nivo + Ipi	Nivo	
Any serious drug-related adverse events						
CA209-067	150/313 (47.9)	25/313 (8.0)	6.00 (4.05, 8.89)	48	8	0.40 (0.34, 0.46)
Any severe adverse events (grade ≥3)						
CA209-067	172/313 (55.0)	51/313 (16.3)	3.37 (2.57, 4.42)	55	16	0.39 (0.32, 0.46)
Adverse events leading to discontinuation						
CA209-067	114/313 (36.4)	24/313 (7.7)	4.75 (3.15, 7.17)	36	8	0.29 (0.23, 0.35)

Source: compiled during the evaluation.

AE = adverse event; CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; Nivo = nivolumab; PFS = progression-free survival; RD = risk difference; RR = risk ratio

*Median follow-up: CA209-067 = 12.2 – 12.5 months.

- 6.31 On the basis of the direct comparison presented by the submission, the comparison of nivolumab plus ipilimumab and nivolumab monotherapy resulted in:
- no conclusions regarding differences in overall survival
 - a statistically significant difference in PFS, with a median difference of approximately 4.60 months favouring nivolumab plus ipilimumab.
- 6.32 On the basis of the direct comparison presented by the submission, for every 100 patients treated with nivolumab plus ipilimumab compared to nivolumab monotherapy:
- approximately 40 more patients experienced serious drug-related adverse events
 - approximately 39 more patients experienced severe (grade three or higher) adverse events
 - approximately 29 more patients experienced adverse events leading to discontinuation of treatment.
- 6.33 Table 11 presents a summary of comparative benefits and harms for the nivolumab plus ipilimumab versus pembrolizumab indirect comparison.

Table 11: Summary of comparative benefits and harms for Nivo + Ipi versus Pembro

Benefits						
OS: CA209-069 nivolumab						
	Nivo + Ipi	Ipi	Absolute difference	HR (95% CI)		
Number of deaths n/N (%)	50/210 (23.8)	96/208 (46.2)				
Median OS (95% CI), months	NR	10.8 (9.3, 12.1)	-	0.42 (0.30, 0.60)		
OS: KN-006- pembrolizumab Q2W						
	Pembro Q2W	Ipi				
Number of deaths n/N (%)	NR	NR				
Median OS (95% CI), months	Not reached	Not reached	-	0.63 (0.47, 0.83)		
OS: KN-006- pembrolizumab Q3W						
	Pembro Q3W	Ipi				
Number of deaths n/N (%)	NR	NR				
Median OS (95% CI), months	Not reached	Not reached	-	0.69 (0.52, 0.90)		
Overall survival - indirect comparison						
Nivo + Ipi vs Pembro Q2W				1.16 (0.40, 3.37)		
Nivo + Ipi vs Pembro Q3W				1.06 (0.54, 2.09)		
PFS - CA209-067 nivolumab						
	Nivo	Ipi				
Number of progressions n/N (%)	151/314 (48.1)	234/314 (74.3)				
Median PFS (95% CI), months	11.5 (8.9, 16.7)	2.9 (2.8, 3.4)	8.6	0.43 (0.35, 0.53)		
PFS - CA209-069 nivolumab						
	Nivo	Ipi				
Number of progressions n/N (%)	42/95 (44.2)	32/47 (68.1)				
Median PFS (95% CI), months	Not reached	3.0 (2.8, 5.1)	-	0.39 (0.25, 0.63)		
PFS pooled – nivolumab				0.42 (0.35, 0.51)		
PFS – KN-006 Pembro Q2W						
	Pembro Q2W	Ipi				
Number of progressions n/N (%)	NR	NR				
Median PFS (95% CI), months	5.5 (3.4, 6.9)*	2.8 (2.8, 2.9)	2.7	0.58 (0.46, 0.72)		
PFS – KN-006 Pembro Q3W						
	Pembro Q3W	Ipi				
Number of progressions n/N (%)	NR	NR				
Median PFS (95% CI), months	4.1 (2.9, 6.9)	2.8 (2.8, 2.9)	1.3	0.58 (0.47, 0.72)		
Indirect comparison PFS – Nivo + Ipi vs Pembro Q2W				0.72 (0.54, 0.97)		
Indirect comparison PFS – Nivo + Ipi vs Pembro Q3W				0.72 (0.55, 0.96)		
Harms						
	Nivo +Ipi	Ipi	RR (95% CI)	Event rate/100 patients**		RD% (95% CI)
				Nivo + Ipi	Ipi	
Any drug-related severe AE (grade ≥3)						
Pooled – Nivo + Ipi	221/407 (54.3)	95/357 (26.6)	2.05 (1.68, 2.49)	54	27	0.28 (0.22, 0.35)
	Pembro	Ipi		Pembro	Ipi	
KN-006 - Pembro	65/ 555 (11.7)	51/ 256 (19.9)	0.59 (0.42, 0.82)	12	20	-0.08 (-0.13, -0.03) ^a
Indirect comparison any drug-related severe AE (graded ≥3) – nivo + ipi vs. pembro						0.36 (0.28, 0.44)^b
Any drug-related AE leading to discontinuation						
	Nivo + Ipi	Ipi		Nivo	Ipi	
Pooled Nivo + Ipi	148/407 (36.4)	50/357 (14.0)	2.59 (1.92, 3.49)	36	14	0.23 (0.17, 0.29)
	Pembro	Ipi		Pembro	Ipi	
KN-006 - Pembro	30/555 (5.4)	24/256 (9.4)	0.58 (0.34, 0.97)	5	9	-0.04 (-0.08, 0.06) ^a
Indirect comparison any AE leading to discontinuation – Nivo+ Ipi vs. Pembro						0.27 (0.18, 0.36)^b

Source: compiled during the evaluation.

AE = adverse event; CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival; Pembro = pembrolizumab; PFS = progression-free survival; RD = risk difference; RR = risk ratio; Q2W = every two weeks;

Q3W = every three weeks

* Incorrectly stated as 5.5 (2.9, 6.9) in the submission.

**Median follow-up in CA209-067: 12.2-12.5 months; minimum follow-up in CA209-069: 11 months; minimum follow-up of KN-006 = 6 months.

^a Calculated during the evaluation using OpenEpi version 2.2.

^b Calculated during the evaluation.

- 6.34 On the basis of the indirect comparison presented by the submission, the comparison of nivolumab plus ipilimumab and pembrolizumab resulted in:
- no statistically significant difference in overall survival
 - a statistically significant difference in PFS favouring nivolumab plus ipilimumab, but the extent of median difference in months of PFS could not be ascertained.
- 6.35 On the basis of the indirect comparison presented by the submission, for every 100 patients treated with nivolumab plus ipilimumab compared to pembrolizumab monotherapy:
- approximately 36 more patients experienced severe drug-related adverse events
 - approximately 27 more patients experienced adverse events leading to discontinuation of treatment.

Clinical claim

- 6.36 The submission described nivolumab plus ipilimumab combination therapy as superior in terms of comparative effectiveness and inferior in terms of comparative safety over the revised main comparator, pembrolizumab monotherapy.
- 6.37 This claim to superior efficacy was based on the indirect comparison of PFS. This claim was weakened for the following reasons:
- differences in eligibility criteria across trials and baseline characteristics that may favour the combination
 - no statistically significant differences in overall survival
 - only an improvement in the objective response rate shown for nivolumab plus ipilimumab over pembrolizumab based on the risk difference, with no statistically significant improvements based on the risk ratio or the odds ratio.
- 6.38 The ESC considered that a claim of superior comparative effectiveness with respect to PFS gain of nivolumab plus ipilimumab combination therapy over pembrolizumab monotherapy may be reasonable, however the magnitude of treatment effect on PFS is uncertain given the issues with exchangeability across the trials. Additionally, the ESC considered there was considerable uncertainty as to whether the magnitude of treatment effect on PFS was a reasonable surrogate for the magnitude of treatment effect on OS in melanoma.
- 6.39 The submission noted that caution must be used in interpreting the safety comparison of nivolumab plus ipilimumab and pembrolizumab, especially where small numbers of patients were being compared. Nevertheless, the submission's claim to inferior safety was supported by:
- statistically significant higher relative risk in the nivolumab plus ipilimumab arms for severe adverse events, adverse events leading to discontinuation, and drug-related adverse events leading to death
 - the PBAC's previous consideration that pembrolizumab was likely non-inferior in

- safety to ipilimumab monotherapy (March 2015 PSD, paragraph 6.44)
 - the evidence suggesting that nivolumab plus ipilimumab is significantly more toxic than ipilimumab monotherapy.
- 6.40 The critical evidence supporting the submission's superior efficacy of nivolumab plus ipilimumab was improved PFS compared to ipilimumab monotherapy and pembrolizumab monotherapy.
- 6.41 The ESC advised that the two most critical pieces of evidence that required consideration were:
- the indirectly supported statistically significant improvement in PFS compared to pembrolizumab, with significant concerns regarding exchangeability of the trials
 - the evidence supporting inferior safety of nivolumab plus ipilimumab compared to pembrolizumab.
- 6.42 The ESC also advised that the potential health benefit based on a surrogate outcome (PFS), with absence of any conclusive evidence based on overall survival also required consideration versus the comparative harms demonstrated with the clinical adverse event data. If the comparative harms outweigh the potential benefits in terms of PFS, then there would be no basis for listing nivolumab plus ipilimumab on either a cost-minimisation or cost-effectiveness basis. If not, then these trade-offs would still need to be carefully and explicitly weighed in an economic model. The current model did not do this (refer to Economic analysis below).
- 6.43 The submission also described nivolumab plus ipilimumab combination therapy as superior in terms of comparative effectiveness and inferior in terms of comparative safety over ipilimumab monotherapy.
- 6.44 This claim of superior efficacy was supported on the basis of PFS only. The only OS data presented (CA209-069) showed no statistically significant improvement in patients treated with combination therapy. The claim of inferior safety was supported by statistically significant differences in:
- serious adverse events
 - severe adverse events (grade ≥ 3)
 - endocrine, gastrointestinal, hepatic or pulmonary events
 - adverse events leading to discontinuation.
- 6.45 The submission described nivolumab plus ipilimumab combination therapy as superior in terms of comparative effectiveness and inferior in terms of comparative safety over one of the submission's additional comparators, nivolumab monotherapy.
- 6.46 Similar to the submission's comparison against ipilimumab monotherapy, this efficacy claim was supported on the basis of PFS only due to the absence of OS data. The submission's safety claim of inferior safety was supported by statistically significant higher frequency of study drug-related adverse events, serious drug-related adverse events, severe-drug related adverse events and drug-related adverse events leading to discontinuation in the nivolumab plus ipilimumab arm of the CA209-067 trial.
- 6.47 The PBAC considered that nivolumab plus ipilimumab demonstrated gains in PFS over pembrolizumab, nivolumab and ipilimumab monotherapies, but was not

convinced that this gain in PFS had a clinically meaningful benefit with regard to estimating any effect on quality of life or predicting any effect on overall survival.

- 6.48 The PBAC considered that nivolumab plus ipilimumab had a significantly worse safety profile compared to pembrolizumab, nivolumab and ipilimumab monotherapies.

Economic analysis

- 6.49 The submission presented 3 cost-utility analyses of nivolumab plus ipilimumab versus ipilimumab, nivolumab and pembrolizumab. All analyses shared the same overall model structure with the economic evaluation presented in the July 2015 nivolumab monotherapy submission, over which the PBAC had expressed many concerns (paragraph 7.5 of the July 2015 Minutes), including:
- the unnecessarily complex approach to modelling the transitions across the usual three health state structure of a model in metastatic cancer
 - only the Akaike information criterion (AIC) statistics were presented for the extrapolated curves used throughout the model; the modelled PFS curves, in particular, appeared to be highly favourable to nivolumab
 - the 10-year time horizon was not strongly supported by the clinical evidence and favoured nivolumab significantly in the economic model
 - the absolute utility values (around 0.8) used for non-progressive and progressive disease states appeared to be high for a population with advanced cancer, and had a significant effect on the ICER.
- 6.50 These issues were considered to be equally applicable to the current model. Table 12 presents a summary of the model structure.

Table 12: Summary of model structure and rationale

Component	Summary
Time horizon	10.12 years in the model base case versus 12.2-12.5 months of median follow up in CA209-067.
Outcomes	LYs and QALYs
Methods used to generate results	Cohort expected value analysis based on log-logistic survival curves extrapolated from CA209-066 data, and the hazard ratio calculated from the indirect comparison of Nivo and Ipi.
Health states	Alive without progressive disease, alive with progressive disease, dead. The model allowed for a splitting of overall survival into pre-progression overall survival and post-progression overall survival.
Cycle length	12 weeks. Half cycle correction applied.
Transition probabilities	PFS transition probabilities were derived from CA209-067 Ipi + Nivo data, and the transition probabilities for other treatments were calculated by applying HRs from the Nivo, Ipi and Pembro comparisons transition probabilities. For OS, a similar process was done with CA209-066 Nivo monotherapy survival curves used as the starting point.

Source: compiled during the evaluation.

Ipi = ipilimumab; HR = hazard ratio; LYs = life-years; Nivo = nivolumab; OS = overall survival; Pembro = pembrolizumab PFS = progression-free survival; QALYs = quality-adjusted life-years.

- 6.51 Of particular concern was the maintenance of the structure of the nivolumab monotherapy model, which included the splitting of overall survival into pre-progression overall survival and post-progression overall survival. The ESC considered that the application of hazard ratios for both PFS and OS resulted in double-counting of the treatment effect. In the comparison against pembrolizumab, setting the HR for OS to 1 increased the ICER over pembrolizumab in the original

submission from around \$75,000/QALY – \$105,000 /QALY to around \$75,000 – \$105,000 /QALY.

6.52 Table 13 presents the key drivers of the model.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Time horizon	10.12 years in the model base case versus 12.2-12.5 months of median follow up	High, favours nivolumab plus ipilimumab
Estimates of hazard ratios	PFS estimates from respective trial data: OS estimates derived by converting from PFS hazard ratios	High, favours nivolumab plus ipilimumab
Application of HRs	Application of hazard ratios for both PFS and OS	High, favours nivolumab plus ipilimumab
Model structure	Splitting overall survival into pre-progression overall survival and post-progression survival	Unclear
Extrapolation curves	Log-logistic curves for PFS and OS	High, favours nivolumab plus ipilimumab
Utility values	High values for model health states, and no utility effects for AEs	High, favours nivolumab plus ipilimumab

Source: compiled during the evaluation.

OS = overall survival; PFS = progression-free survival

- 6.53 The model relied on overall survival hazard ratios derived from progression-free survival hazard ratios. This conversion was based on a Pearson correlation coefficient of PFS and OS hazard ratios in melanoma trials sourced from Flaherty 2014. The PSCR (p.2) asserted that evidence from Flaherty et al 2014, and emerging data from PD-1 immunotherapy clinical trials (CA209-066 and KN-006) support a positive link between PFS and OS. The ESC considered that the evidence used in the submission to support the correlation between PFS and OS in melanoma (Flaherty et al 2014), had several methodological limitations that biased the analysis in favour of a correlation.
- 6.54 The Pearson correlation is only a measure of the variation between data points and the line of best fit. It is not, and cannot be used as, the slope of the line of best fit. The submission misinterpreted the Pearson coefficient as a slope of log transformed line of best fit. This misinterpretation was the critical component of the submission's strategy to convert PFS hazard ratios to OS hazard ratios, and so the generated OS hazard ratios were largely deemed invalid. The PSCR (p.5) provided a recalculated regression line from the Pearson coefficient data of Flaherty et al 2014, which the sponsor claimed was a 4-5% lower factor compared to using the correlation co-efficient and resulted in marginally higher ICERs.
- 6.55 The submission also relied on the overall survival curve of nivolumab monotherapy from CA209-066 to populate overall survival curves for all treatments. The PBAC had expressed concerns regarding this extrapolation in the July 2015 Meeting (PBAC July 2015 nivolumab minutes, paragraph 7.5). Notably, the model did not use Kaplan Meier trial-based data followed by extrapolated curves.
- 6.56 The submission also maintained the same time horizon as the nivolumab monotherapy model, 10 years, which the PBAC did not consider to be strongly supported (paragraph 6.36 of the July 2015 Minutes). The submission did not provide additional support for this model duration, and the model remained sensitive to the

time horizon.

- 6.57 The length of the maintenance phase of nivolumab plus ipilimumab in the economic model assumed only 7 doses of nivolumab, compared to 16.65 in the financial estimates. This significantly underestimated incremental costs in the model. The PSCR (p.5) noted that this was also changed in the revised economic evaluation to reflect the maximum mean duration of nivolumab monotherapy in CA209-003, which was the basis of the financial estimates.
- 6.58 The submission stated that utility values were derived from CA209-067 EQ-5D data, but the clinical study report did not mention EQ-5D results. The utility values in the model were similar to the nivolumab monotherapy submission, which the PBAC had considered to be high for melanoma patients (July 2015 PBAC Minutes, paragraph 7.5). Since the safety claim of nivolumab plus ipilimumab was one of inferior safety, the incorporated utility values favoured nivolumab plus ipilimumab treatment. The ESC also noted that adverse event costs were included in the model, but not associated disutilities.
- 6.59 The table below presents the results of the economic evaluation for all three comparisons – versus ipilimumab, versus nivolumab and versus pembrolizumab. All costs were based on the drug costs used in the submission and were not altered to reflect the July 1 2015 Sixth Community Pharmacy Agreement (6CPA) changes and DPMA costs. Inclusion of these alterations to drug cost would have had minimal impact on model results.

Table 14: Results of the economic evaluation

Component	Nivo + Ipi		Ipi		Increment	
	Original submission	Sponsor revision	Original submission	Sponsor revision	Original submission	Sponsor revision
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	3.290	3.290	1.299	1.299	1.991	1.991
Incremental cost/QALY vs. Ipi:					\$ [REDACTED]	\$ [REDACTED]
Component	Nivo + Ipi		Nivo		Increment	
	Original submission	Sponsor revision	Original submission	Sponsor revision	Original submission	Sponsor revision
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	3.290	3.290	1.995	1.995	1.295	1.295
Incremental cost/QALY vs. Nivo:					\$ [REDACTED]	\$ [REDACTED]
Component	Nivo + Ipi		Pembro		Increment	
	Original submission	Sponsor revision	Original submission	Sponsor revision	Original submission	Sponsor revision
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	3.290	3.290	2.058	2.058	1.232	1.232
Incremental cost/QALY vs. Pembro:					\$ [REDACTED]	\$ [REDACTED]

Source: 'Appendix 1 and 2 Nivo_ipi combo model revised.xlsx' and 'Appendix 1 Section D – Combo vs nivo and ipi model.xlsx.' and 'Appendix 2 Section D – Combo vs pembro model.xlsx'

Ipi = ipilimumab; Nivo = nivolumab; Pembro = pembrolizumab; QALY = Quality adjusted life-year

Note: incremental costs and incremental QALYs were presented in 1000 person totals in the model. These values were divided by 1000 (individual patient average values) during the evaluation for clarity.

- 6.60 Acknowledging that the submission was lodged before the nivolumab monotherapy PBAC Minutes had been made available to the sponsor, the issues identified by the PBAC, particularly those regarding model structure were not addressed in current

submission. These structural issues, combined with a lack of valid overall survival estimates, and unrealistic assumptions regarding nivolumab plus ipilimumab treatment costs and time horizon, rendered the results unlikely to accurately represent the cost-effectiveness of nivolumab plus ipilimumab combination therapy.

Drug cost/patient/course: \$ [REDACTED], including mark-ups and fees.

6.61 A summary of the estimated drug cost/patient/course of nivolumab plus ipilimumab is presented in the table below. Based on the estimates presented in the submission, and the assumption of cost-parity of pembrolizumab and ipilimumab (\$ [REDACTED]/patient/course), the drug cost/patient/course for nivolumab plus ipilimumab was [REDACTED] times greater than that of pembrolizumab.

Table 15: Summary of drug costs/patient/course for nivolumab plus ipilimumab

Drug	Parameter	Source	Number of vials and doses	Drug costs per infusion	Drug costs per patient
Combination phase					
Nivo	Doses per patient	Combination phase CA209-067: Q3W	4.0	\$ [REDACTED] (ex-man) \$ [REDACTED] (as dispensed)	\$ [REDACTED] (as dispensed)
	Vials per admin	Ipilimumab patient registry (ACOL) mean weight for nivolumab patients: 81.4kg	40mg/4ml: 0; 100mg/10ml: 1		
Ipi	Doses per patient	Combination phase CA209-067	4.0	\$ [REDACTED] (as dispensed)	\$ [REDACTED] (as dispensed)
	Vials per admin	Ipilimumab patient registry (ACOL) mean weight for nivolumab patients: 81.4kg	50mg/10mL: 0.88 200mg/40mL: 1.00		
Maintenance phase					
Nivo	Doses per patient	Nivolumab monotherapy mean dose from CA209-003 (20.65) less 4 doses.	16.65	\$ [REDACTED] (ex-man) \$ [REDACTED] (as dispensed)	\$ [REDACTED] (as dispensed)
	Vials per admin	Ipilimumab patient registry (ACOL) mean weight for nivolumab patients: 81.4kg	40mg/4ml: 1.11 100mg/10ml: 2.0		
TOTAL:		\$ [REDACTED] with no rebate			

Source: Compiled during the evaluation,

Admin = administration; Kg = kilogram; mg= milligram; ml = millilitre

Note: the revised estimates presented total treatment costs including administration costs as the drug acquisition cost per infusion. This error was corrected in the evaluation.

6.62 Although the approach in the revised Section D to calculate nivolumab plus ipilimumab costs based on the ipilimumab per patient cost reduced the combination drug cost per infusion, the new approach also removed the [REDACTED]% rebate applied to combination therapy in the original submission, leading to a higher price of \$ [REDACTED] in the revised submission compared to \$ [REDACTED] after the rebate in the original submission.

Estimated PBS usage & financial implications

6.63 This submission was not considered by DUSC. The submission presented two scenarios for estimating the financial implications of listing nivolumab plus ipilimumab:

- Scenario 1: First-line treatment or second-line treatment after dabrafenib ± trametinib. This stated scenario was not what was specified in the submitted financial estimates and treatment algorithm in the submission body and the submission's financial model. This model and its estimates assumed no

nivolumab plus ipilimumab treatment beyond the first line. The PSCR (p.6) acknowledged that the financial estimates for Scenario 1 were not aligned with the proposed patient pool for this scenario, and clarified that Scenario 2 was the base case.

- Scenario 2: Any treatment line (aligning with the proposed TGA restriction and requested PBS listing). This was the approach to calculate the base case financial implications.
- 6.64 For both of the scenarios presented, the submission used the same approach as applied in the nivolumab monotherapy submission to estimate the eligible population. The PBAC had noted that those estimates appeared to be high (July 2015 PBAC Minutes, paragraph 6.46).
- 6.65 The 6th Community Pharmacy Agreement (6CPA) which took effect on 1 July 2015, made some changes to the way chemotherapy preparation fees are paid under the Section 100 Efficient Funding of Chemotherapy (EFC) arrangement.
- 6.66 In addition, some chemotherapy compounders will be paid a smaller fee and the DPMA that is published in the schedule will only include that smaller fee.

Under the finalised new arrangements:

- a) the preparation fees paid to compounders who are licensed by the TGA to undertake such compounding are higher than those paid to compounders who are not licensed by the TGA, recognising that TGA licensed compounders incur additional costs in complying with the TGA's licensing requirements, as compared to chemotherapy compounders who are not TGA licensed
 - b) the preparation fee paid to TGA licensed compounders remains the same as under the 5th CPA at \$102.67 (indexed price for 2014/2015)
 - c) the preparation fees paid to a s90 Community Pharmacy (incl s92 approved practitioners) and a s94 Approved Private Hospital Authority are the same as those paid to TGA licensed compounders to recognise the specialist nature of preparing chemotherapy medicines
 - d) the preparation fee paid to non-TGA licensed compounders is \$20 less at \$82.67
 - e) where applicable, the \$20 portion of the preparation fee will be paid directly to the compounder through Australian Healthcare Associates (AHA)
 - f) the \$20 is not currently captured by the DPMA that is published in the Schedule of Pharmaceutical Benefits.
- 6.67 As the majority of chemotherapy preparations are compounded in settings where the \$102.67 fee applies, this fee should continue to be used in PBAC submissions.
- 6.68 The table below provides a summary of the estimated use and financial implications of the requested listing of nivolumab plus ipilimumab provided in the updated Section E. Prices were updated during the evaluation to reflect costs based on the 6CPA which came into effect on 1 July 2015.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 2 – proposed base case as per PSCR					
Overall net cost to PBS/RPBS	\$	\$	\$	\$	\$
Cost to government for MBS	\$891,849	\$926,263	\$960,332	\$995,827	\$1,032,601
Cost to government of AE treatment	\$691,187	\$717,828	\$744,281	\$771,736	\$800,226
Original commentary estimates	\$	\$	\$	\$	\$
Overall net cost to health budget	\$	\$	\$	\$	\$

Source: compiled during the evaluation

- 6.69 The submission’s estimates were not considered accurate, for the following reasons:
- The submission’s estimates include the assumption that nivolumab monotherapy would receive a positive recommendation at the July 2015 PBAC meeting and therefore cost offsets for nivolumab monotherapy would apply. These cost offsets will only occur if nivolumab monotherapy is PBS-listed. While cost offsets that the submission had applied to substitution of nivolumab monotherapy would instead occur through substitution of pembrolizumab, the value of the offsets would be less given that pembrolizumab is assumed to have the same cost per patient as ipilimumab.
 - As stated above, the submission maintained the same methodology in estimating the size of the eligible patient population as used in the nivolumab monotherapy submission. Since pembrolizumab has achieved listing and since nivolumab plus ipilimumab combination therapy has a potentially different treatment algorithm than nivolumab monotherapy (or ipilimumab monotherapy), it is unclear if using the ipilimumab-treated population of 800 would be appropriate in the current context, but the current submission may have overestimated the eligible population. The ESC noted that these estimates do not capture patients who have been enrolled in early access programs etc.
 - The submission’s estimate of 16.65 doses of nivolumab in the maintenance phase is over two times greater than the estimate of 7.0 doses used in the economic evaluation. The estimate of 16.65 doses is based on the nivolumab monotherapy arm of trial CA209-003, a phase 1 dose escalation study for nivolumab monotherapy. While CA209-067 is ongoing and therefore cannot provide accurate estimates of the duration of use, estimates based on CA209-003 are not likely to be reliable given that it was for nivolumab monotherapy and thus included no combination phase. In the Pre-PBAC Response (p3), the sponsor “acknowledges that the likely duration of therapy may not be the same as in CA209-003, however suggests that this is a better approximation of likely duration than that predicted by study CA209-067 (due to the length of follow up of patients). The sponsor is open to discussions on this point to achieve the same price per patient as proposed while ensuring that the duration of therapy and therefore the financial estimates are reflective of likely clinical use.”
 - adverse event costs were likely underestimated.
- 6.70 The submission did not provide any sensitivity analyses of its financial estimates, on the basis that the presentation of Scenario 2 would cover most uncertainties given it allows unrestricted use of nivolumab plus ipilimumab. Given that Scenario 2 actually represented the requested restriction for combination therapy, sensitivity analyses of this scenario would have been informative, although interpretation of the results must take into consideration the concerns listed above with formulation of the submission’s estimates.

- 6.71 Although the submission's estimates were not considered to be accurate, a sensitivity analysis consistent with the PBS restriction for pembrolizumab (use in first line in wild-type patients and second line in *BRAF*-mutant patients) conducted during the evaluation indicated estimated costs to be \$20 million – \$30 million in year 1 increasing to \$30 million – \$60 million in year 5, slightly less than the estimates provided by the submission for unrestricted use in any line of therapy.

Quality use of medicines

- 6.72 The submission provided a summary of the sponsor's plans regarding quality use of medicines. These plans comprised the same components that were provided for the nivolumab monotherapy submission and included:
- physician experience with nivolumab
 - clinical trial activity in Australia
 - expanded access program (EAP) for nivolumab monotherapy. The submission stated that 'currently' there was 262 patients enrolled, but did not specify a date for the observation. No indication was given as to whether these patients would be grandfathered under the requested restriction. No program for combination therapy was mentioned
 - education initiatives supporting nivolumab use
 - the submission indicated the customer support model used for ipilimumab is also intended to be used for the nivolumab plus ipilimumab combination.

Financial management – risk sharing arrangements

- 6.73 The submission did not include any provisions of a potential managed entry scheme (MES). The submission included a proposed special pricing arrangement (SPA), which included two parts:
- a published versus effective price with a rebate proposed to accommodate the difference
 - a capped arrangement designed to offset residual risk associated with higher than expected expenditure outside proposed reimbursed use. No details were provided regarding the specifics of such arrangement.

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

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend the combination of nivolumab and ipilimumab for the treatment of unresectable or metastatic (Stage III or Stage IV) melanoma for listing on the PBS. In reaching this conclusion, the PBAC noted that the use of combination immunotherapy was associated with a modest improvement in PFS, but a substantial increase in adverse events. The net clinical benefit of combination treatment was therefore uncertain.
- 7.2 In considering the clinical need for the nivolumab and ipilimumab combination treatment, the PBAC noted that the components of the regimen are already available for use via the PBS as sequential monotherapy. Also the current least toxic and most

effective option, pembrolizumab, is already PBS-listed as first-line therapy. At the November 2015 PBAC meeting, nivolumab was accepted as similar to pembrolizumab and thus two PD-1 inhibitors have been accepted for PBS-listing (see item 7.14 from the November 2015 PBAC meeting).

- 7.3 The PBAC considered that the revised main comparator, pembrolizumab monotherapy, was appropriate. The PBAC noted that the management of melanoma was rapidly evolving and considered the sequential use of a PD-1 inhibitor followed by ipilimumab, and dabrafenib ± trametinib for *BRAF* mutant patients, were also appropriate comparators. The PBAC noted that no data or analyses were provided to support the proposed positioning of the combination ahead of dabrafenib ± trametinib for *BRAF* mutant patients.
- 7.4 The PBAC noted that the combination therapy showed an improvement in median PFS of 4.6 months compared to nivolumab monotherapy in the trial CA209-067, however the clinical significance of this gain had not been adequately demonstrated either in terms of an improvement in quality of life or as a valid surrogate for OS. The PBAC also noted that progression in the trials was determined by meeting RECIST criteria based largely on repeated images taken of the tumours, which may not be as relevant or meaningful an outcome to the patient as progression which manifests with symptoms. The PBAC noted that adjustment was made in the assessment of PFS by the trials for the phenomenon of “pseudo-progression” (where the immunotherapy may induce an early increase in the size of tumours), but could not be confident that this adjustment was long enough for all patients, nor how such an inadequacy might bias the comparisons across these immunotherapies. The PBAC noted that no estimate of median PFS was available from the weaker indirect comparison of the combination therapy and pembrolizumab. However, there was no basis not to conclude that it would be similar to the 4.6 months for the comparison with nivolumab, given the similarity of the hazard ratios (0.74, 95% CI: 0.60, 0.92, for the direct comparison of the combination with nivolumab monotherapy and 0.724, 95% CI: 0.54, 0.97, for the indirect comparison of the combination with pembrolizumab monotherapy) and PBAC’s separate conclusion of non-inferiority between pembrolizumab and nivolumab monotherapy (see item 7.14 from the November 2015 PBAC meeting). The PBAC also noted that there were no statistically significant differences in OS between combination nivolumab and ipilimumab treatment and either pembrolizumab or ipilimumab monotherapy, and no OS data yet officially reported comparing the combination with nivolumab monotherapy.
- 7.5 The PBAC considered that combination treatment with nivolumab and ipilimumab has a significantly inferior safety profile compared to pembrolizumab monotherapy, nivolumab monotherapy or ipilimumab monotherapy. The PBAC noted that there were significantly higher rates of serious adverse events with nivolumab plus ipilimumab combination therapy compared to the monotherapies, with the combination treatment having, for example, an odds ratio of 6.27 (95% CI: 4.42, 8.89) for any severe adverse event over nivolumab monotherapy, and an odds ratio for discontinuations due to drug-related adverse events of 6.90 (95% CI: 4.32, 11.01) over nivolumab monotherapy. The PBAC was also concerned by early reports of endocrine toxicity, with the possibility of irreversible diabetes.
- 7.6 The PBAC noted the ESC’s view of the submission’s economic model, and agreed that neither the model, nor its resulting ICER could be relied upon. It was noted that

the model shared the same overall structure as the economic evaluation presented in the July 2015 nivolumab monotherapy submission, over which the PBAC had expressed many concerns, including:

- the absence of alternative survival extrapolations, particularly where Kaplan-Meier data could be used during the trial period
- the unnecessarily complex approach to modelling the transitions across the usual three health state structure of a model in metastatic cancer which resulted in the double-counting of the treatment effect
- only the Akaike information criterion (AIC) statistics were presented for the extrapolated curves used throughout the model; the modelled PFS curves, in particular, appeared to be highly favourable to nivolumab
- the 10-year time horizon was not sufficiently supported by the clinical evidence and favoured nivolumab significantly in the economic model
- the absolute utility values used for non-progressive and progressive disease states appeared to be high for a population with advanced cancer, and had a significant effect on the ICER.

- 7.7 The PBAC considered that the financial impact of listing the combination treatment was highly uncertain, with the original submission estimating a net cost to the health budget of over \$30 – \$60 million per annum, and the revised Section E estimating over \$60 – \$100 million per annum. The cost per patient was also uncertain due to the parallel submission affecting the cost of nivolumab.
- 7.8 The PBAC considered that any resubmission should be a major submission to allow for evaluation of an improved economic model and updated mature overall survival data.
- 7.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

While disappointed with the PBAC decision, the sponsor is working proactively with all relevant stakeholders in an effort to ensure timely PBS listing of nivolumab + ipilimumab combination therapy for Australian patients with metastatic melanoma.