

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**

1 Purpose of Application

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

2 Requested listing

2.1 The requested restriction is 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.

Name, Restriction, Manner of administration and form	Max. Amount	No.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial			\$ [REDACTED] (public effective price)	Opdivo [®] BQ
nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	5	\$ [REDACTED] (private effective price)	

Initial treatment - BRAF V600 mutation negative

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

Public Summary Document – July 2015 PBAC Meeting

Clinical criteria:	<p>The treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p>The condition must not have been treated previously with a <i>PD-1 inhibitor nivolumab</i>; OR <i>Patient must have developed intolerance to another PD-1 inhibitor of a severity necessitating permanent treatment withdrawal</i></p> <p>AND</p> <p><i>The condition must be negative for a BRAF V600 mutation.</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 of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks.</p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>Special Pricing Arrangements apply.</i></p>

Initial treatment - BRAF V600 mutation positive

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

Public Summary Document – July 2015 PBAC Meeting

Clinical criteria:	<p>The treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p>The condition must not have been treated previously with a <i>PD-1 inhibitor nivolumab</i>; OR <i>Patient must have developed intolerance to another PD-1 inhibitor of a severity necessitating permanent treatment withdrawal</i></p> <p>AND</p> <p><i>The condition must be positive for a BRAF V600 mutation</i></p> <p>AND</p> <p><i>The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) unless contraindicated or not tolerated according to the TGA approved Product Information.</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 of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks.</p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>Special Pricing Arrangements apply.</i></p>

Continuing treatment

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:	Continuing
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>Patient must have previously been issued with an authority prescription for this drug</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p>Patient must have stable or responding disease.</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	The recommended dose of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. No increase in the maximum number of repeats may be authorised. <i>Special Pricing Arrangements apply.</i>

- 2.2 The requested listing differs from the PBAC-recommended PBS listing for pembrolizumab (see the positive recommendations from the March 2015 meeting), which was recommended to be for patients who have not been exposed to ipilimumab, with the sponsor of pembrolizumab providing subsidised access to pembrolizumab for patients who are refractory to ipilimumab.
- 2.3 The submission sought listing on the basis of a cost utility analysis compared to ipilimumab, via an indirect comparison.
- 2.4 Although the submission indicated there were approximately 180 patients currently in an expanded access program, there was no discussion in the submission of grandfathering provisions for these patients. In the PSCR, the sponsor noted that, should nivolumab be recommended for listing, patients accessing nivolumab via the sponsor's Expanded Access Program, who are deriving clinical benefit, should be grandfathered across to PBS-subsidised nivolumab.

3 Background

- 3.1 TGA status at time of PBAC consideration: no TGA documentation was available.
- 3.2 Nivolumab was submitted to the TGA on 7 January 2015 and there was no TGA documentation available at the time of evaluation. The submission indicated that the current submission was being made under "extreme" parallel processing (submission's highlighting). There was no indication provided in the submission if the anticipated date of registration in February 2016 will be moved forward in regard to extreme parallel processing.
- 3.3 This was the first consideration of nivolumab by the PBAC. Another PD-1 inhibitor, pembrolizumab, was considered by the PBAC in March 2015, and the PBAC has also recently considered ipilimumab (November 2012), vemurafenib (March 2013), dabrafenib (July 2014) and trametinib (November 2014) for the treatment of unresectable Stage III or Stage IV metastatic melanoma.
- 3.4 The submission indicated that the sponsor was planning to lodge a submission in July 2015 for combination nivolumab and ipilimumab therapy.

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

4 Clinical place for the proposed therapy

- 4.1 The requested listing specified monotherapy treatment of unresectable Stage III or Stage IV malignant melanoma in previously untreated patients (BRAF wild-type) as well as monotherapy treatment in patients who have progressed on or after a BRAF inhibitor regimen or after ipilimumab therapy (BRAF mutant). It was anticipated that, for BRAF wild-type patients, 95% of patients would use PD-1 inhibitors (nivolumab or pembrolizumab) in the first-line setting, replacing ipilimumab. For BRAF mutant patients, 95% of patients would receive dabrafenib ± trametinib as first-line therapy and PD-1 inhibitors would be used as second-line therapy, replacing ipilimumab.
- 4.2 Noting the forecast submission expected to be lodged in July 2015 (for the November 2015 PBAC meeting) for combination use of nivolumab and ipilimumab, the ESC considered that the treatment of malignant melanoma is a rapidly evolving area, and it was likely that the treatment algorithm depicted in the current submission would change in the near future.

5 Comparator

- 5.1 The submission nominated ipilimumab as the main comparator. The PSCR maintained that ipilimumab is still the appropriate main comparator “as i) it is the only immuno-oncology medicine currently PBS listed for the treatment of unresectable or metastatic melanoma and ii) head-to-head data comparing nivolumab with ipilimumab are available.” While this was the appropriate comparator at the time the submission was lodged, the ESC considered that the recommendation of pembrolizumab in March 2015 by the PBAC (albeit in ipilimumab-naïve patients only) meant that pembrolizumab would also be an appropriate comparator because nivolumab and pembrolizumab are closer pharmacological analogues than either is to ipilimumab and the availability or not of evidence is irrelevant to the determination of the main comparator. The ESC requested that a comparison of the nivolumab and pembrolizumab submissions be prepared for the PBAC.
- 5.2 The submission presented what was described as an informal comparison of nivolumab and pembrolizumab. The informal comparison presented by the submission consisted solely of tabled evidence from the nivolumab trial CA209-066 and two pembrolizumab trials, KN-001 and KN-006, with no statistical comparisons provided. Therefore, the informal comparison presented by the submission did not represent an actual comparison that could inform the comparative effectiveness and safety of nivolumab and pembrolizumab. The PSCR provided an indirect comparison of pembrolizumab and nivolumab (based on CA209-067 and KN-006 data).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (12), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the importance of access to melanoma treatments on the PBS and the survival benefits of nivolumab compared to current treatment with chemotherapy or ipilimumab.

Original submission (11 March 2015)

Clinical trials

6.3 The original submission was based on an indirect comparison of one trial (CA209-066) comparing nivolumab and dacarbazine (DTIC) and a second trial (MDX010-20) comparing ipilimumab and gp100. The submission claimed that since DTIC and gp100 both represent largely ineffective therapies, they represent a common reference. Given that gp100 was used as a proxy for DTIC and fotemustine in the original (July 2011) and subsequent ipilimumab submissions (March 2012, November 2012), this was considered reasonable.

6.4 Details of the trials presented in the submission are provided in the table below.

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

Trial	Description	Reports
Common reference DTIC and gp100		
Nivolumab		
CA209-066	R, DB, MC	A Phase 3, Randomized, Double-blind Study of BMS-936558 (Nivolumab) Versus Dacarbazine in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma. 20-Oct-2014. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372(4):311-9.
Ipilimumab		
MDX010-20	R, DB, MC	A Randomized, Double-blind Multicenter Study Comparing MDX-010 Monotherapy, MDX-010 in Combination with a Melanoma Peptide Vaccine, and Melanoma Vaccine Monotherapy in HLA-A*0201-Positive Patients with Previously Treated Unresectable Stage III or IV Melanoma. Mar-2010. Hodi FS, O'Day SJ, McDermott DF, Weber RW, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010a; 363(8): 711-23. Weber JS, Dummer R, de Pril V, Lebbé C, et al. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer. 2013; 119(9):1675-82.

Source: Table 9, p48-50, Table 11, p55-56 of the submission.

DB=double-blind; DTIC=dacarbazine; gp100=melanoma antigen glycoprotein 100 peptide vaccine; MC=multicentre; R=randomised

6.5 The submission excluded CA209-037, which is a randomised, open-label trial comparing nivolumab with DTIC or carboplatin+paclitaxel in patients progressing post anti-CTLA-4 (ipilimumab) therapy. The submission indicated the main reason for

excluding this trial was that there was limited information available and the trial was still ongoing. The submission indicated that while data for overall response rate has been presented (at ESMO 2014), data for overall survival was not yet available. In addition, the trial included patients who had failed prior therapy with ipilimumab. The submission stated that patients most likely to receive nivolumab in the second-line setting would be those who have failed on BRAF inhibitors, which this trial did not inform. However, the trial protocol indicated that BRAF mutant patients must have progressed on ipilimumab and a BRAF inhibitor, and the data presented at ESMO indicated that 22% of the trial population were BRAF mutant. Importantly, the requested PBS listing specified patients who have progressed on or after a BRAF inhibitor regimen or after ipilimumab therapy. While CA209-037 appeared to have included BRAF mutant patients who had failed both a BRAF inhibitor and ipilimumab, it also included patients who had failed ipilimumab, which was a relevant patient population for the requested PBS listing. With a trial completion date of January 2015, it was assumed that data additional to that presented at ESMO 2014 would be available. Inclusion of this trial would have been informative for the requested PBS listing.

- 6.6 The key features of the randomised trials used in the indirect comparison are summarised in the table below.

Table 2: Summary of trials used in the clinical evaluation

Trial ID	N	Comparison	Trial design	Primary outcome	Use in the economic evaluation
Nivolumab vs. DTIC					
CA209-066	411	Nivo 3mg/kg Q2W ^a n=210 DTIC 1000mg/m ² Q3W n=208	Phase III R, DB, MC	Overall survival	Extrapolated survival data
Ipilimumab vs. gp100					
MDX010-20	676	IPI 3mg/kg Q3W+gp100 n=403 IPI 3mg/kg Q3W ^a n=137 gp100 n=136	Phase III R, DB, MC	Overall survival	Indirect HRs for PFS and OS applied to nivolumab transition probabilities

^a In the CA209-066 trial, nivolumab was administered with DTIC-matched placebo IV Q3W and DTIC was administered with nivolumab-matched placebo IV Q2W. In the MDX010-20 trial, ipilimumab monotherapy and gp100 monotherapy were administered with gp100 placebo or ipilimumab placebo, respectively.

DB=double-blind; gp100=glycoprotein 100 peptide vaccine; HR=hazard ratio; IPI=ipilimumab; MC=multicentre; Nivo=nivolumab; Q2W=every 2 weeks; Q3W=every 3 weeks; R=randomised

Source: compiled during the evaluation

- 6.7 Given that the data lock for CA209-066 occurred prior to the protocol amendment which allowed DTIC-treated patients to cross-over to nivolumab post progression, and there was no cross-over in the MDX010-20 trial, outcomes are not confounded by cross-over.
- 6.8 Although the overall risk of bias within the two randomised, double-blind trials was low, the risk of bias across the indirect comparison of CA209-066 and MDX010-20 was high. These trials were poorly exchangeable, for the following reasons:
- Patients in the nivolumab trial CA209-066 had less severe disease (64.4% with ECOG=0 across both arms of CA209-066 compared to 53.3% with ECOG=0 in the ipilimumab trial MDX010-20). Of additional concern was the imbalance in ECOG status within the nivolumab trial, with 70.5% of patients in the nivolumab arm with ECOG=0 compared to 58.2% in the DTIC arm.
 - Patients in CA209-066 had shorter duration of disease. While this concurred with the requirement that the patients were treatment naïve compared to MDX010-20,

which required that patients had received at least one prior systemic therapy, it also suggested patients in CA209-066 were healthier than those in MDX010-20.

- The duration of follow-up in CA209-066 was 16 months. In contrast, the duration of follow-up as reported in the MDX010-20 CSR was 55 months. In neither case is it clear whether this was the mean or median or (more likely) longest duration of follow-up. Nevertheless, the clearly longer duration of follow-up in the ipilimumab trial would favour nivolumab noting PBAC has elsewhere concluded that hazard ratios tend to become less favourable over time.
- While MDX010-20, in previously treated patients, was used as the pivotal clinical evidence in the ipilimumab submissions (July 2011, March 2012, November 2012), and therefore use of this evidence had previously been accepted by the PBAC in a first-line scenario, it was likely that relevant differences remain between previously treated and previously untreated populations. In particular, evidence available in Schadendorf 2015 (meta-analysis of 10 randomised trials and 2 observational studies) indicated that first-line ipilimumab treatment is more effective than second-line treatment. Consequently, an indirect comparison between a first-line trial (CA209-066) and a second-line trial (MDX010-20) is likely to be biased in favour of the first-line trial.
- CA209-066 included only BRAF wild-type patients. BRAF status was not assessed at the time of the ipilimumab trial and it could not be determined what proportions of the MDX010-20 population were BRAF wild-type or BRAF mutant. The submission presented an analysis of objective response rate comparing 217 BRAF wild-type and 74 BRAF mutant patients and claimed this demonstrated there was no evidence to suggest the effect of nivolumab observed in BRAF wild-type patients would be different to that seen in BRAF mutant patients. The applicability of this comparison to the requested listing could not be determined. The submission argued that the difference in BRAF status was not relevant to the modelled evaluation as it focused on BRAF wild-type patients. The key issue was that the clinical claim based on BRAF wild-type patients was applied to BRAF mutant patients; and the modelled results were also applied to BRAF mutant patients, given the anticipated use of nivolumab in BRAF mutant patients following the failure of a BRAF inhibitor. The PSCR stated that this data was drawn from a study (Larkin et al, JAMA Oncology, February 2015), which demonstrated no difference in PFS rates in a meta-analysis of four studies when comparing wild-type or mutant BRAF patients treated with nivolumab monotherapy. The ESC noted that the meta-analysis was a retrospective analysis of non-randomised cohorts and may not be reliably applicable to the requested PBS population given the data was drawn from three Phase I studies (one bio-marker study, one dose-ranging study and one concurrent or sequenced ipilimumab and nivolumab study) and one Phase III study (CA209-037) in patients who had ≥ 2 previous systemic treatments. Additionally, the sub-groups in the meta-analysis were small.

Comparative effectiveness

- 6.9 Table 3 provides the results of the indirect comparison of nivolumab and ipilimumab, for PFS and OS.

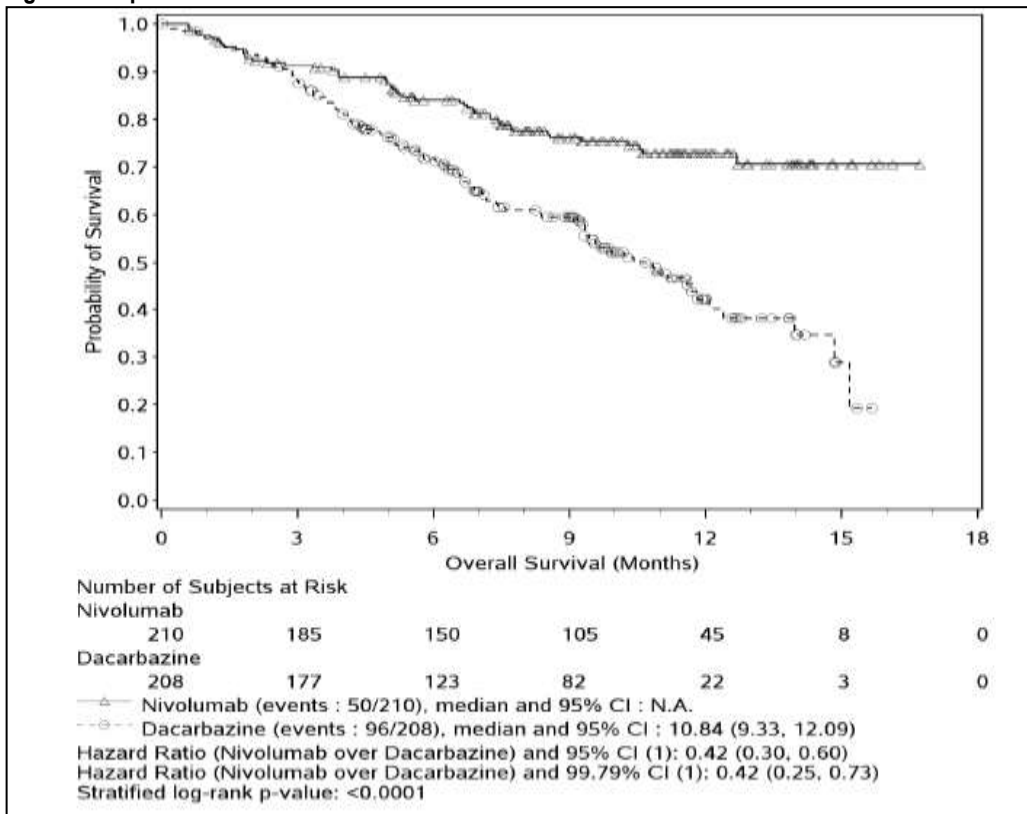
Table 3: Indirect comparison: OS and PFS CA209-066 and MDX010-20

	Nivo n/N (%)	DTIC n/N (%)	Absolute difference	HR (95% CI)
Overall survival - CA209-066 - nivolumab				
Death	50/210 (23.8%)	96/208 (46.2%)	-	0.42 (0.30, 0.60)
OS median months	NR	10.84 (9.33, 12.09)	-	-
Overall survival - MDX010-20 - ipilimumab				
	Ipi n/N (%)	gp100 n/N (%)		
Death	100/137 (73.0%)	119/136 (87.5%)	-	0.66 (0.51, 0.87)
OS median months	10.12 (8.02, 13.80)	6.44 (5.49, 8.71)	3.68	-
Indirect comparison overall survival - nivo vs. ipi				0.64 (0.41, 0.99)
Progression-free survival - CA209-066 - nivolumab				
	Nivo n/N (%)	DTIC n/N (%)		
Progressed	108/210 (51.4%)	163/208 (78.4%)	-	0.43 (0.34, 0.56)
PFS median months	5.06 (3.48, 10.81)	2.17 (2.10, 2.40)	2.89	-
Progression-free survival - MDX010-20 - ipilimumab				
	Ipi n/N (%)	gp100 n/N (%)		
Progressed	122/137 (89.1%)	127/136 (93.4%)	-	0.64 (0.50, 0.83)
PFS median months	2.86 (2.76, 3.02)	2.76 (2.73, 2.83)	0.10	-
Indirect comparison progression-free survival - nivo vs. ipi				0.67 (0.47, 0.96)

Source: Table 23, p87; Table 24, p88; Table 25, p90 and Table 26, p91 of the submission
DTIC=dacarbazine; HR=hazard ratio; Ipi=ipilimumab; Nivo=nivolumab

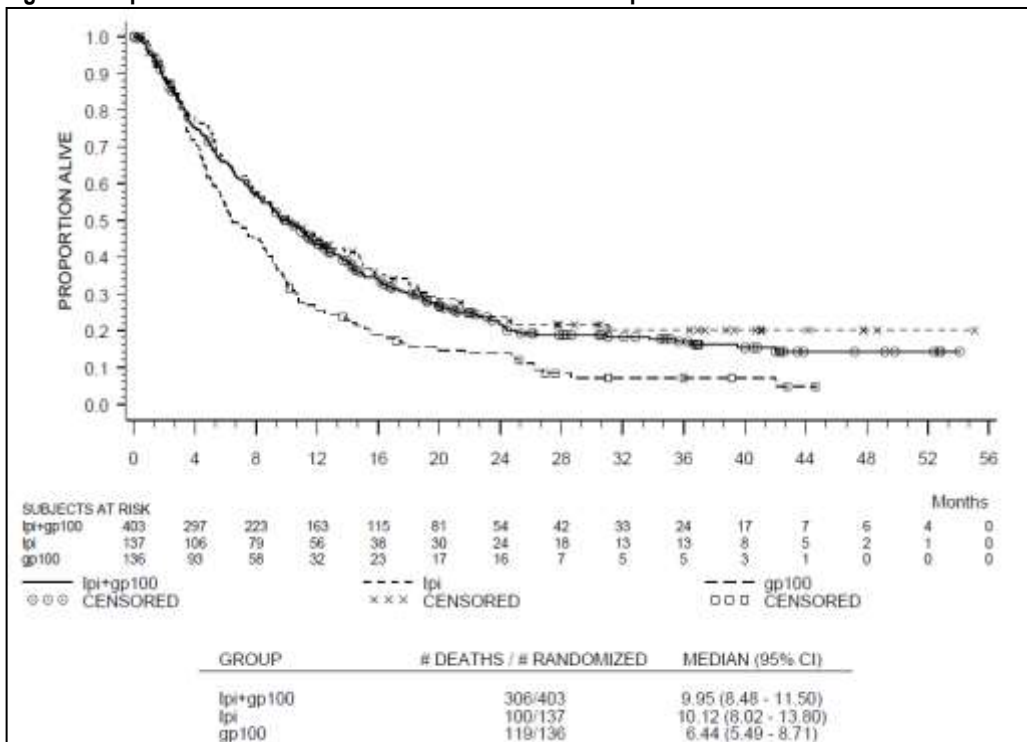
- 6.10 The indirect comparisons indicated a statistically significant advantage for nivolumab compared to ipilimumab for OS and PFS. The results of both analyses had borderline significance, with the upper confidence limits close to 1 (0.99 for OS; 0.96 for PFS). Interpretation of these results was hindered by the poor exchangeability between the trials, particularly the healthier population in the nivolumab trial.
- 6.11 Overall survival curves from the nivolumab and ipilimumab trials are provided below. The submission claimed that comparison of the nivolumab and ipilimumab arms in the curves suggest that nivolumab appears to be superior. The time frame of the figures was different, with the nivolumab Kaplan-Meier curve extending over 16 months and the ipilimumab curve over 55 months.

Figure 1: Kaplan-Meier curves overall survival CA209-066 - nivolumab



Source: Figure 9, p86 of the submission

Figure 2: Kaplan-Meier curves overall survival MDX010-20 - ipilimumab



Source: Figure 10, p87 of the submission

- 6.12 The submission presented an informal comparison of nivolumab and pembrolizumab in an attachment to the submission. This informal comparison consisted solely of tabled data from CA209-066 for nivolumab and KN-001 and KN-006 for pembrolizumab. No statistical comparisons of the data were provided, nor was there any discussion of similarities and differences between the trials. As such, the comparison presented by the submission was limited.

Comparative harms

- 6.13 The submission did not provide any statistical comparisons of adverse events (AEs) on the basis that “....the respective control arms included in the trials are unsuitable proxies for a common comparator”. The submission presented only a naïve comparison of safety outcomes and claimed that the safety of nivolumab is overall more favourable than that of ipilimumab. Given that the same trials, with the same comparators, are used for the submission’s indirect comparison of efficacy outcomes, the submission’s rationale for not conducting an indirect comparison could not be supported. It was assumed that the premise was that DTIC has greater toxicity than gp100, and therefore an indirect comparison was not appropriate. The same difference across comparators should also have been applied to efficacy. To maintain consistency with the submission’s approach to efficacy outcomes, indirect comparisons of safety outcomes were conducted during the evaluation and determined that the submission’s conclusion of more favourable safety for nivolumab could not be statistically supported across all outcomes. Table 4 below provides a summary of adverse events.

Table 4: Summary of indirect comparison^a of nivolumab and ipilimumab – safety outcomes

Safety outcome	Nivolumab vs. DTIC (N=411)	Ipilimumab vs. gp100 (N=263)	Indirect comparison
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Overall drug-related AEs			
Any AE	0.98 (0.88, 1.10)	1.03 (0.91, 1.16)	0.96 (0.55, 1.67)
Discontinued due to AE	0.71 (0.23, 2.21)	3.27 (1.09, 9.80)	0.22 (0.05, 1.05)
Any severe AE (graded ≥3)	0.66 (0.41, 1.07)	2.14 (1.24, 3.69)	0.31 (0.15, 0.64)
Diarrhoea	1.99 (0.18, 21.84)	6.05 (0.74, 49.73)	0.33 (0.01, 8.00)
Colitis	NC	NC	-
Any serious AE	1.05 (0.57, 1.94)	4.84 (1.89, 12.31)	0.22 (0.07, 0.67)
Select AEs with potential immunologic etiology			
Any severity			
Any AE	1.53 (1.27, 1.84)	1.94 (1.46, 2.58)	0.79 (0.56, 1.11)
Endocrine	6.30 (1.89, 21.00)	5.04 (1.12, 22.62)	1.25 (0.18, 8.58)
Gastrointestinal	1.20 (0.84, 1.70)	2.07 (1.26, 3.39)	0.58 (0.32, 1.06)
Hepatic	1.35 (0.70, 2.62)	0.84 (0.26, 2.69)	1.61 (0.42, 6.15)
Skin	1.91 (1.45, 2.53)	2.26 (1.50, 3.39)	0.85 (0.52, 1.39)
Severe			
Any AE	2.32 (1.09, 4.95)	5.29 (1.86, 15.02)	0.44 (0.12, 1.59)
Gastrointestinal	4.98 (0.58, 42.33)	11.08 (1.45, 84.96)	0.45 (0.02, 8.62)
Hepatic	2.19 (0.77, 6.20)	0.34 (0.04, 3.20)	6.52 (0.54, 78.14)

^a Statistical analyses conducted during the evaluation.

Source: Submission Table 29, p.95; Table 31, p.98; Table 32,p.99; Table 33,p101 of the submission; CA209-066 CSR Table 8.7.1-1, p118; Table 8.7.3-1, p126; Table 8.7.6-1, p137; Table 8.7.7-1, p118 of the CA209-066 CSR; MDX010-20 CSR Table 7.21.1 of the MDX010-20 CSR.

AE=adverse event

- 6.14 The submission claimed that there were fewer serious AEs overall for nivolumab, and in particular diarrhoea, colitis and fatigue; that there were fewer severe AEs, in particular diarrhoea and colitis; and there were fewer severe AEs with a potential immunologic cause, in particular gastrointestinal and hepatic events. The analyses conducted during the evaluation (see Table 4 above) indicated that only one claim made by the submission was supported – fewer serious AEs overall. There were also statistically significantly fewer severe AEs graded ≥ 3 with nivolumab, although the rates of diarrhoea and colitis events reported were too low to assess claims of advantages for nivolumab for these specific events, which the submission emphasised. There were also no statistically significant differences in all other specific AEs cited by the submission, i.e. severe AEs with a potential immunologic cause, AEs leading to discontinuation, and serious AEs of diarrhoea, colitis and fatigue.
- 6.15 Given the poor exchangeability of the two trials (e.g. ipilimumab patients had a longer duration of advanced disease) and the shorter period of follow-up considered for safety outcomes in the nivolumab trial, the safety results did not clearly demonstrate that nivolumab safety was superior to that of ipilimumab.

Benefits/harms

- 6.16 A summary of benefits and harms based on the indirect comparison of nivolumab and ipilimumab is provided in the table below. Interpretation of these results was hindered by the poor exchangeability between the trials.

Table 5: Summary of comparative benefits and harms for nivolumab and ipilimumab – indirect comparison

Benefits						
OS: CA209-066 nivolumab						
	Nivo n/N (%)	DTIC n/N (%)	Absolute difference	HR (95% CI)		
Death	50/210 (23.8%)	96/208 (46.2%)	-	0.42 (0.30, 0.60)		
OS median months	NR	10.84 (9.33, 12.09)	-	-		
OS - MDX010-20 - ipilimumab						
	Ipi n/N (%)	gp100 n/N (%)				
Death	100/137 (73.0%)	119/136 (87.5%)	-	0.66 (0.51, 0.87)		
OS median months	10.12 (8.02, 13.80)	6.44 (5.49, 8.71)	3.68	-		
Indirect comparison OS – nivo vs. ipi						0.64 (0.41, 0.99)
PFS - CA209-066 nivolumab						
	Nivo n/N (%)	DTIC n/N (%)				
Progressed	108/210 (51.4%)	163/208 (78.4%)	-	0.43 (0.34, 0.56)		
PFS median months	5.06 (3.48, 10.81)	2.17 (2.10, 2.40)	2.89	-		
PFS - MDX010-20 - ipilimumab						
	Ipi n/N (%)	gp100 n/N (%)				
Progressed	122/137 (89.1%)	127/136 (93.4%)	-	0.64 (0.50, 0.83)		
PFS median months	2.86 (2.76, 3.02)	2.76 (2.73, 2.83)	0.10	-		
Indirect comparison PFS – nivo vs. ipi						0.67 (0.47, 0.96)
Harms^a						
	Nivo	DTIC	RR (95% CI)	Event rate/100 patients		RD% (95% CI)
				Nivo	DTIC	
Any drug-related severe AE (graded ≥3)						
CA209-066 nivo	24/206	36/205	0.66 (0.41, 1.07)	11.7	17.6	-
	Ipi	gp100		Ipi	gp100	
MDX010-20 - ipi	34/131	16/132	2.14 (1.24, 3.69)	26.0	12.1	-
Indirect comparison any drug-related severe AE (graded ≥3) – nivo vs. ipi						-19.7 (-31.3, -8.2)
Any drug-related serious AE						
	Nivo	DTIC		Nivo	DTIC	
CA209-066- nivo	19/206	18/205	1.05 (0.57, 1.94)	9.2	8.8	-
	Ipi	gp100		Ipi	gp100	
MDX010-20 - ipi	24/131	5/132	4.84 (1.89, 12.31)	18.3	3.8	-
Indirect comparison any drug-related serious AE – nivo vs. ipi						-14.1 (-23.3, -4.9)

^a Statistical analyses conducted during the evaluation.

Source: Compiled during the evaluation

- 6.17 On the basis of the indirect evidence presented by the submission, the comparison of nivolumab and ipilimumab resulted in:
- Statistically significant differences in OS and PFS that have borderline significance (upper 95% CLs of 0.99 and 0.96, respectively). Differences in months of median OS and PFS could not be ascertained.
- 6.18 On the basis of the indirect comparison presented by the submission, every 100 patients treated with nivolumab in comparison to ipilimumab resulted in:
- Approximately 20 fewer patients with treatment-related severe adverse events (grade ≥3);
 - Approximately 14 fewer patients with treatment-related serious adverse events.

Pre-Sub-Committee Response (27 May 2015)

- 6.19 The PSCR (Table 1, p2) provided early results from CA209-067 (further information about this trial was published by Larkin et al, NEJM, 31 May 2015), a phase III,

randomised, double-blind trial which included a direct comparison of nivolumab monotherapy and ipilimumab monotherapy in patients with previously untreated unresectable or metastatic melanoma. The ESC considered that this trial would likely provide a more robust comparison because it did not obviously suffer from the exchangeability issues that existed with the indirect comparison across CA209-066 and MDX010-20 and it also stratified patients as having BRAF mutations (31.5%) or not (68.5%), but also noted that the information presented about this trial was limited.

Table 6: Results of the nivolumab and ipilimumab monotherapy arms in CA209-067

	Nivolumab, N=316	Ipilimumab, N=315	HR (95% CI)
Overall survival			
Death	NR	NR	██████████
OS median months	NR	NR	
Progression-free survival			
Progressed	NR	NR	0.57 (0.47, 0.70)
PFS median months	NR	NR	
Overall response			RR (95% CI)
Complete response	28/316 (8.9%)	7/315 (2.2%)	3.99 (1.77, 8.99)
Partial response	110/316 (43.8%)	53/315 (16.8%)	2.07 (1.55, 2.76)
Stable disease	34/316 (10.8%)	69/315 (21.9%)	0.49 (0.34, 0.72)
Progressive disease	119/316 (37.7%)	154/315 (48.9%)	0.77 (0.64, 0.92)
Unable to determine	25/316 (7.9%)	32/315 (10.2%)	0.78 (0.47, 1.28)
Objective response rate	138/316 (43.7%)	60/315 (19.0%)	2.29 (1.77, 2.97)
Total deaths	85 ^a (27.2%)	114 ^a (36.7%)	0.74 (0.59, 0.94)
Cause of death			
Disease	72 ^a (23.0%)	102 ^a (32.8%)	0.70 (0.54, 0.91)
Study drug toxicity	1 (0.3%)	1 (0.3%)	0.99 (0.06, 15.82)
Other	12 (3.8%)	16 (4.2%)	0.75 (0.62, 1.55)
Drug-related adverse events ^b			
Total events	257/313 (82.1%)	268/311 (86.2%)	0.95 (0.89, 1.02)
Grade 3-4 total events	51/313 (16.3%)	85/311 (27.3%)	0.60 (0.44, 0.81)
Diarrhoea	60/313 (19.2%)	103/311 (33.1%)	0.58 (0.44, 0.76)
Grade 3-4 diarrhoea	7/313 (2.2%)	19/311 (6.1%)	0.37 (0.16, 0.86)
Colitis	4/313 (1.3%)	36/311 (11.6%)	0.11 (0.04, 0.31)
Grade 3-4 colitis	2/313 (0.6%)	27/311 (8.7%)	0.07 (0.02, 0.31)

^a It is not clear what N is used as 85/316 provides a percentage of 26.9% and 114/315 results in a percentage of 36.2%. Similar discordance with the percentages occurs with cause of death due to disease.

^b the Ns for adverse events were not provided in the PSCR, but were obtained from the Larkin 2015 NEJM paper.

HR=hazard ratio; NR=not reported; RR=relative risk

Source: Table 1, p2 of the PSCR, as "Analysis using IPD, database lock: 17-Feb-2015, CSR expected mid-June 2015"

6.20 The PSCR also provided an indirect comparison of efficacy and safety based on CA209-067 for nivolumab and KN-006 for pembrolizumab using ipilimumab as the common reference. The ESC noted that, for the outcomes presented, there were no statistically significant differences between nivolumab and pembrolizumab, with the exception of colitis, with the difference favouring nivolumab. However, given the limited information available to assess the exchangeability of these two trials, including whether the duration of follow-up was similar across the data analysed from the two trials, the ESC advised that the indirect comparison did not provide a strong basis to reach conclusions.

Table 7: Indirect comparison of nivolumab and pembrolizumab based on CA209-067 and KN-006

	CA209-067 nivolumab vs. ipilimumab	KN-006 pembrolizumab vs. ipilimumab	Indirect nivo vs. pembro
Benefits	HR (95% CI)		
Overall survival		0.69 (0.52, 0.90)	
Progression-free survival	0.57 (0.47, 0.70)	0.58 (0.47, 0.72)	0.99 (0.74, 1.32)
Harms	RR (95% CI)		
Total drug-related AEs	0.95 (0.89, 1.02)	1.00 (0.90, 1.11)	0.95 (0.84, 1.08)
Diarrhoea	0.58 (0.44, 0.76)	0.64 (0.44, 0.92)	0.91 (0.57, 1.44)
Colitis	0.11 (0.04, 0.31)	0.44 (0.21, 0.92)	0.25 (0.07, 0.88)

AE=adverse event; HR=hazard ratio; RR=relative risk

Source: Table 2, p3 of the PSCR

Clinical claim

6.21 The submission describes nivolumab as superior in terms of comparative efficacy and superior in terms of comparative safety over ipilimumab. The ESC considered that this claim was not adequately supported by the indirect comparison presented by the submission, for the following reasons:

- The trials used in the indirect comparison, CA209-066 for nivolumab and MDX010-20 for ipilimumab, were poorly exchangeable (see paragraph 6.8, above).
- The observed differences in OS and PFS had borderline statistical significance, with upper 95% confidence limits of 0.99 and 0.96, respectively.
- Statistically significant differences were observed for two safety outcomes, any severe drug-related AE (grade ≥ 3) and any serious AE. No statistically significant differences were observed for individual adverse events.

Overall, there was not strong support for the claimed superiority of nivolumab over ipilimumab on the basis of the clinical evidence presented. The submission also assumed that the observed results, based on BRAF wild-type patients in CA209-066 and MDX010-20, where BRAF status was unknown, would apply to BRAF mutant patients. The ESC considered that there was no strong support for this assumption, given the lack of conclusive evidence that BRAF status does or does not have consequences for outcomes in this setting.

6.22 The ESC considered that data from trial CA209-067 would likely provide stronger support for the submission's clinical claim of superior comparative efficacy and safety over ipilimumab, but noted that the information about this trial and its results were limited and still emerging.

6.23 The submission provided no substantive basis upon which to judge the comparative effectiveness and safety of nivolumab and pembrolizumab. The ESC considered that the indirect comparison across trials CA209-067 and KN-006 provided support for a conclusion of similar effectiveness and safety between nivolumab and pembrolizumab, but noted that the information about this comparison and its results were limited and still emerging.

Economic analysis

6.24 The submission presented a cost-utility analysis of nivolumab versus ipilimumab. The analysis was based on a claim of superior efficacy and safety for nivolumab which is limited by the poor exchangeability of the trials included in the indirect

comparison. The following table provides a summary of the structure and rationale of the model.

Table 8: Summary of model structure and rationale

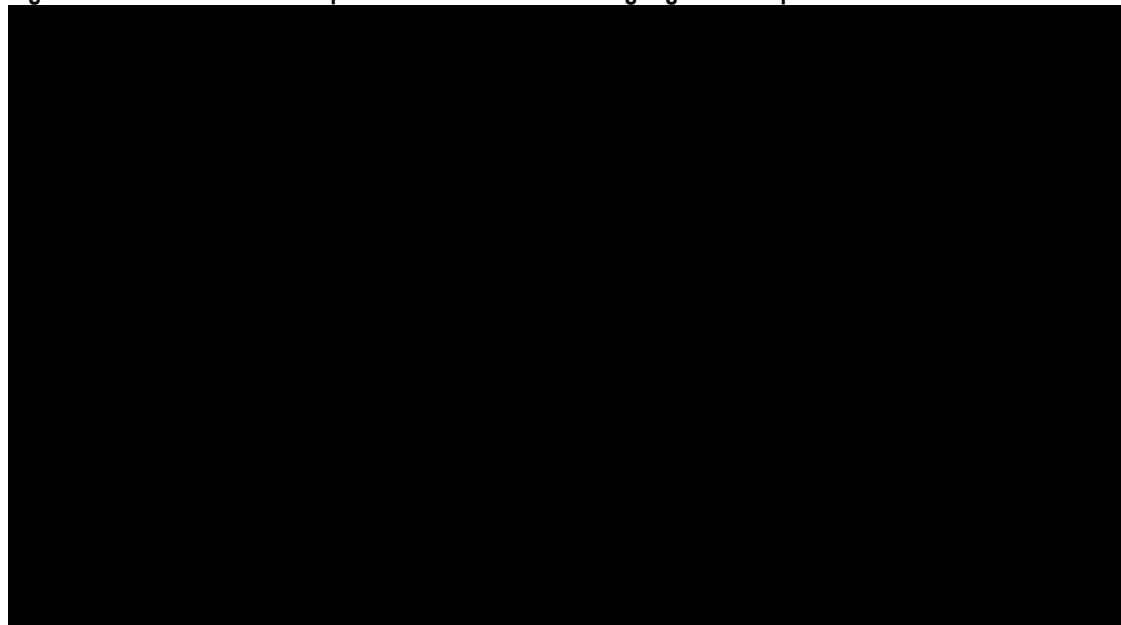
Component	Summary
Time horizon	10 years in the model base case versus 16 months in CA209-066
Outcomes	LYs and QALYs
Methods used to generate results	Cohort expected value analysis based on log-logistic survival curves extrapolated from CA209-066 data, and the hazard ratio calculated from the indirect comparison of nivolumab and ipilimumab.
Health states	Non-progressive disease, progressive disease and death.
Cycle length	9 weeks for the first cycle, and 12 weeks for subsequent weeks. Half cycle correction applied.
Transition probabilities	Nivolumab transition probabilities derived from log-logistic extrapolation of CA209-066 data. Ipilimumab transition probabilities were calculated by applying hazard ratios from the indirect nivolumab-ipilimumab comparison to nivolumab transition probabilities.

Source: compiled during the evaluation. LYs=life-years; QALYs=quality-adjusted life-years.

- 6.25 The difference between the utilities in the non-progressive disease and progressive disease health states in the model was small, however the difference in disease costs between the two health states was large, therefore the ICER was driven by survival differences. To examine how the survival differences drive the model, the model was tested by increasing the OS hazard ratio of 0.636 in the base case to 0.986 (the upper 95% confidence limit which corresponds to almost no OS effect); this counter-intuitively only increased the ICER/QALY from \$45,000 - 75,000 to \$45,000 - 75,000. The reason for this was not clear, and likely related to structural issues with the model, but it appeared that there may be double-counting of the treatment effect built into the way the transition probabilities in the model were constructed. Even if double-counting did not occur, this counter-intuitive anomaly would still be of concern because the unnecessarily complex approach taken to modelling the transitions across the usual three health state structure of a model in metastatic cancer prevented the generation of a satisfactory alternative explanation.
- 6.26 The model split OS into “pre-progression OS” and “post-progression OS”. No explanation or justification was provided for this split. The model combined these two facets of OS although there appeared to be resultant inconsistencies within the model. For example, the probabilities of death and PFS exceed 1.0. This was corrected in the submission by down-adjusting the probability of death. However, even though this down-adjustment was made, the model produced more deaths for ipilimumab-treated patients when the hazard ratio for OS was set to 1.0 (and thus there should be no incremental life-years gained, and the number of deaths should be equal between nivolumab and ipilimumab). It appeared that the combination of the extrapolations for pre- and post-progression of OS resulted in this counter-intuitive outcome. It thus appeared that the splitting of the area under the OS curves biased the model in favour of nivolumab.
- 6.27 The curves in the figure below informed the baseline transition probabilities, to which the OS hazard ratio was applied to transition probabilities extracted from both of the OS curves - the “pre-progression” and “post-progression” transition probabilities to “dead” – and a PFS hazard ratio was applied to the PFS transition probabilities from

“progression-free” to “progression”. This suggested that survival gains were driven by both increased PFS and OS.

Figure 3: Nivolumab transition probabilities derived from log-logistic extrapolation of CA209-066 data



Source: Appendix B, Section D of the submission

- 6.28 Mortality from the “non-progressive disease” state also appeared to be double counted: separate transition probabilities to the “progressive disease” and “dead” states were extracted from the fitted PFS and OS curves, respectively.
- 6.29 The ESC concern was due to the fact that, in the same model:
- a progression-free survival hazard ratio was applied to PFS;
 - a hazard ratio for aggregate OS was applied to pre-progression OS; and
 - a hazard ratio for aggregate OS was applied to post-progression OS.
- 6.30 Applying a hazard ratio to PFS reduced the likelihood of progression, whilst applying the hazard ratio for aggregate OS to post-progression OS (there was no hazard ratio for post-progression OS) increased the effect of progression. The aggregate OS was a function of PFS, pre-progression OS, and post-progression OS. The hazard ratio for PFS should be applied independently of the hazard ratio for aggregate OS.
- 6.31 The ESC therefore considered that it was difficult to adapt the model to provide a robust estimate of the ICER. An alternative approach with the same original data might be to generate separate time-to-event curves for time to progression (censoring for mortality) and time to death, from which time in the non-progressive and progressive states could be estimated.
- 6.32 The ESC noted that the model applied the inverse of the hazard ratio to the nivolumab transition probabilities for death to generate the ipilimumab transition probabilities for death. The treatment effects were assumed to be maintained for the duration of the model time horizon (10 years), which was considered unlikely, and favoured nivolumab. The ESC considered that an alternative approach with the

same original data might be to estimate separate hazard ratios for time to progression and for overall survival, and then apply the estimated hazard ratios to the respective curves for the time period over which the ratios were estimated (e.g. 16 months in the CA209-066 study). Beyond 16 months, the time to progression, and overall survival curves could be set to converge over the remainder of the model's time horizon. Alternative model time horizons should be specified to test the effects of alternative times to convergence (e.g. 5, 7, and 10 years).

- 6.33 The economic evaluation was limited to the population in CA209-066, the BRAF wild-type population. As discussed above, there was limited evidence demonstrating there are no differences in efficacy and safety of nivolumab for BRAF wild-type and BRAF mutant patients. Since the requested restriction includes use in BRAF mutant patients, there is not a strong basis on which to extend the model results to that population.
- 6.34 The difference in utilities between the non-progressive and progressive states was small, but the ESC noted that the absolute utility values – around 0.8 – appeared to be high for a population with advanced cancer. These absolute utility values had a significant effect on the ICER, because they drive the QALY gains associated with the estimated survival gain.
- 6.35 Key drivers of the model are identified in the table below.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Time horizon	10 years; assumed from 16-month CA209-066 trial duration	High, favours nivolumab
Indirect comparison hazard ratio for OS	0.636	High, favours nivolumab
Extrapolation method	Log-logistic survival curves; splitting of OS	High, favours nivolumab

Source: compiled during the evaluation. OS=overall survival

- 6.36 The 10-year time horizon favoured nivolumab significantly in the economic model. Given that the clinical information (Schadendorf 2015) supporting 10-year ipilimumab survival was limited; that the efficacy data of nivolumab beyond 4 years was limited; and that the model assumed significant survival benefit of nivolumab over ipilimumab throughout the 10-year duration, the 10-year time horizon is not strongly supported by the clinical evidence. The model was sensitive to the time horizon (see below).
- 6.37 The model extrapolated progression-free survival and overall survival from log-logistic curves for the entirety of the model and not a post-trial (16 month) extrapolation phase. The submission did not present sensitivity analyses exploring alternative extrapolation curves or methods, nor did it present sensitivity analyses using Kaplan-Meier estimates for the trial period, followed by curve-generated transition probabilities in the post-trial extrapolation period. Sensitivity analyses could not be run during the evaluation for alternate extrapolation methods, but it was reasonable to assume that the model was highly sensitive to the extrapolation method. The PSCR claimed that the log-logistic parametric distribution was selected based on face validity and goodness of fit statistics. The ESC also considered that directly using the Kaplan-Meier trial based data followed by extrapolated curves in the model would be informative.

6.38 The following table provides the results of the modelled evaluation.

Table 10: Results of the economic evaluation

Component	Nivolumab	Ipilimumab	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/life-year gained			\$ [REDACTED]
Incremental cost/QALY			\$ [REDACTED]
Sensitivity analyses from the PSCR*			Incremental cost/QALY
CA209-067 data			\$ [REDACTED]
Updated infusion costs			\$ [REDACTED]
7 year time horizon			\$ [REDACTED]

Source: 'Appendix B Section D – Nivolumab March 2015 PBAC.xlsx', Table 3, p3 of the PSCR

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.

*The PSCR provided no details as to how the variables in the economic model were changed, therefore these sensitivity analyses could not be verified independently.

6.39 ESC considered that it was likely that the incremental cost per QALY presented in the base case analysis was significantly underestimated and did not accurately represent the cost-effectiveness of nivolumab over ipilimumab, for the following reasons:

- The unnecessarily complex approach taken to modelling the transitions across the usual three health state structure of a model in metastatic cancer resulted in counter-intuitive results when tested in sensitivity analyses which could not be readily explained.
- While there was not enough information to determine whether the log-logistic extrapolation method was systematically biased in one direction or another, the lack of sensitivity analyses employing alternative curves was of concern. In addition, the model did not use Kaplan-Meier trial-based data followed by extrapolated curves, and instead used solely modelled curves. Overall, it was difficult to ascertain the sensitivity of the model to various extrapolation methods, and whether the extrapolated effect modelled in the submission could reasonably be expected in the Australian population. The ESC noted that only the Akaike information criterion (AIC) statistics were presented for the extrapolated PFS and post-progression OS curves used throughout the model. The PFS curve, in particular, appeared to be highly favourable to nivolumab. The ESC considered that the best fitting Weibull, log-logistic, exponential and Gompertz curves should be presented for each of the observed OS, PFS and post-progression survival data and the economic model re-run using different extrapolation methods for these outcomes to examine the model's sensitivity to the extrapolation method selected.
- The treatment effects relied upon for the extrapolations used in the model were derived from an indirect comparison of poorly exchangeable trials that was likely to be biased in favour of nivolumab (healthier trial patients).
- The time horizon of 10 years, which was not adequately justified, significantly favoured nivolumab.
- The model did not incorporate costs of patients continuing nivolumab treatment beyond progression. As there are no explicit restrictions for patients continuing treatment post-progression in the requested restriction, these costs could be considerable. Omission of these costs likely favoured nivolumab significantly.

The ESC also noted that the model assumed no further lines of therapy, e.g. ipilimumab as second-line therapy following first-line nivolumab therapy.

- 6.40 The results of the presented sensitivity analyses demonstrated that the model was most sensitive to time horizon (increasing the incremental cost/QALY from \$45,000 - \$75,000 to \$45,000 - \$75,000 for a 5-year horizon and to \$45,000 - \$75,000 for a 7-year time horizon), and estimates of hazard ratios between ipilimumab and nivolumab (increasing the incremental cost/QALY to \$45,000 - \$75,000 when using the upper 95% CL of the OS hazard ratio – although the ESC noted that this was a counter-intuitively small increase, see paragraph 6.25). Multivariate analyses changing both these two variables simultaneously increased the incremental cost/QALY to \$75,000 – \$105,000 over 5 years and \$45,000 - \$75,000 over 7 years. A change in time horizon and use of the Australian population weight (sponsor's data), which increased vial usage, had a significant impact on the incremental cost/QALY (7-year time horizon and weight of 82.1kg: \$45,000 - \$75,000; 5-year time horizon and weight of 82.1kg: \$75,000 – \$105,000).
- 6.41 These analyses would only be valid if the extrapolation method was justified and accepted, and if it was determined that the proportion of patients receiving nivolumab post-progression in the proposed Australian population would be negligible.
- 6.42 Given that direct randomised trial evidence was now available, and noting the PBAC preference for economic evaluations that directly reflect the trial data before using modelling to extrapolate beyond the median duration of follow-up in the trials (see, for example, the description of the economic evaluation requested for the Managed Entry Scheme resubmission in the November 2014 PSD for trametinib), the ESC advised that it would be informative to adopt the PBAC-preferred approach directly.

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

- 6.43 A summary of the estimated drug cost/patient/course for nivolumab and ipilimumab is presented in the table below. Based on the estimates presented in the submission, the drug cost/patient/course for nivolumab was [REDACTED]% greater than that of ipilimumab.

Table 11: Summary of drug costs/patient/course for nivolumab and ipilimumab

Parameter	Source	Number of vials and doses	Drug cost/admin	Drug cost/patient/course
Nivolumab				
Doses per patient	CA209-003: 3mg/kg arm: mean duration of treatment = [REDACTED]	[REDACTED] (dosing every 2 weeks)	\$ [REDACTED] ^a	\$ [REDACTED] ^a
Vials per admin	CA209-066: mean weight for nivolumab patients: [REDACTED]	40mg/4ml: [REDACTED] vials; 100mg/10ml: [REDACTED] vials		
Ipilimumab				
Doses per patient	MDX010-20 + 4% re-induction rate (sponsor data)	3.54 doses	\$ [REDACTED]	\$ [REDACTED]
Vials per admin	Assumption: same as nivolumab: [REDACTED]	50mg/10ml: [REDACTED] vials; 200mg/40ml: [REDACTED] vials		

^a Based on an effective price of \$ [REDACTED] for the 100mg/10ml vial and \$ [REDACTED] for the 40mg/ml vial. Discrepancies were apparent in the written text of the submission and the spreadsheet inputs for the cost per administration for nivolumab and ipilimumab. While the spreadsheet inputs were consistent with the derivation of nivolumab and ipilimumab costs in Tables 70 and 71, differing costs (\$ [REDACTED] and \$ [REDACTED], respectively) were presented in Table 80 of the submission. Source: Table 70, p177; Table 71, p177, Table 75, p180 and Table 76, p181 of the submission.

6.44 It was unlikely that the estimated nivolumab drug cost/patient/course was of sufficient reliability given the following issues:

- The submission appropriately acknowledged that nivolumab treatment in clinical practice may be longer than that observed in the pivotal trial CA209-066 (■■■■ doses) given the limited 12-month follow-up. The submission used longer-term data from a phase I dose escalation trial (CA209-003) to estimate nivolumab treatment duration. Although the use of long-term data may be more suitable, the reliability of the estimated mean duration treatment from CA209-003 was affected by limited recruitment (3mg/kg treatment arm: n=17) and inadequate applicability of the trial participants (previously treated with ipilimumab).
- Appropriateness of using average patient weight from CA209-066 to determine the number of nivolumab vials per administration: the average weight observed in CA209-066 (■■■■ kg) was lower than that observed in the ipilimumab-treated PBS population of 82.1 kg. Furthermore, the lack of consideration for patient weight distribution and associated vial wastage affected the accuracy of the number of nivolumab vials used per patient.

Estimated PBS usage & financial implications

6.45 This submission was not considered by the DUSC. Estimated use and financial implications are presented in the table below.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab treated patients	■■■■	■■■■	■■■■	■■■■	■■■■
Nivolumab cost	\$■■■■	\$■■■■	\$■■■■	\$■■■■	\$■■■■
Substituted therapies ^a	-\$■■■■	-\$■■■■	-\$■■■■	-\$■■■■	-\$■■■■
Net cost to the PBS/RPBS	\$■■■■	\$■■■■	\$■■■■	\$■■■■	\$■■■■
Net administration costs	\$■■■■	\$■■■■	\$■■■■	\$■■■■	\$■■■■
Net cost to health budget	\$■■■■	\$■■■■	\$■■■■	\$■■■■	\$■■■■

^a The submission indicated that nivolumab will substitute for ipilimumab, dabrafenib and chemotherapy (fotemustine used as a proxy) for the treatment of unresectable or metastatic melanoma.

Source: Table 89, p195; Table 90 p196; Table 94, p200 and Table 98, p206 of the submission.

The redacted table above shows that the estimated use and financial implications of nivolumab to the health budget for the treatment of unresectable Stage III or Stage IV malignant melanoma is less than 10,000 patients per year and more than \$100 million per year in each of the first five years of listing.

6.46 While the epidemiological approach was consistent with methods used in the ipilimumab November 2012 resubmission, given that it is expected that nivolumab will be in the same therapeutic area as ipilimumab, it was unclear why a market share analysis was not incorporated in the financial model. Analysis of ipilimumab PBS utilisation data by the Department has indicated a stable uptake of approximately less than 10,000 patients per year since commencement of listing in August 2013. Given that the financial model calculated over three times as many patients initiating nivolumab (increasing from less than 10,000 in year 1 to less than 10,000 in year 5), there was inadequate external validity associated with the submission’s estimates. On this basis, it was likely that the net costs to Government (more than \$100 million

per year over 5 years) were substantially overestimated by the submission. In its PSCR, the sponsor argued that the estimated patient numbers cited in its submission were representative of expected PD-1 inhibitor (i.e. nivolumab, pembrolizumab and other future PD-1 inhibitors) utilisation, and that current standard of care for BRAF wild-type and mutant patients (ipilimumab and dabrafenib ± trametinib) would be completely displaced. The PSCR also claimed that there would be an influx of patients who would traditionally be enrolled in clinical trials. The ESC agreed that the expected numbers of patients treated with nivolumab (or across all PD-1 inhibitors in the future) were overestimated. The ESC therefore considered that it would also be informative for the sponsor to provide information on the number of Australian patients with unresectable Stage III or Stage IV malignant melanoma enrolled across all of its trials on a month-by-month basis since the listing of ipilimumab.

- 6.47 Sensitivity analyses limiting the nivolumab treated population to be the same as the uptake for ipilimumab in year 1, increasing in subsequent years according to the projected growth in the incident melanoma population (Cancer in Australia an overview, AIHW & ACCR 2012: chapter 2, supplementary table D2.5), estimated lower overall net costs of \$–more than \$100 million per year over 5 years.

Quality Use of Medicines

- 6.48 The submission provided a summary of the sponsor's plans regarding the quality use of medicines. Details were provided on:
- Physician experience with nivolumab;
 - Clinical trial activity in Australia;
 - Expanded access program. As of 28 February 2015, there were 187 patients enrolled, 7 discontinued and 8 patients with pending applications. No indication was provided by the submission as to whether these patients would be grandfathered under the requested restriction (the PSCR indicated patients deriving clinical benefit in the sponsor's Expanded Access Program should be grandfathered);
 - Education initiatives supporting nivolumab use;
 - The submission indicated the customer support model used for ipilimumab is intended to also be used for nivolumab.

Financial Management – Risk Sharing Arrangements

- 6.49 The submission asserted that a managed entry scheme (MES), identified as a managed access program (MAP) in the submission, was not required for nivolumab as the sponsor did not consider there to be significant clinical uncertainties that would necessitate the need for separate provision or collection of survival data, as has been done for ipilimumab. Given the uncertainty regarding the clinical benefit of nivolumab (see Clinical claim above) and the resultant uncertainty surrounding the estimate of cost-effectiveness, it appears that there may be potential for a MES to be established, to allow for provision of directly comparative data from a nearly completed direct randomised trial along with a revised cost-effectiveness estimate. The PSCR provided results from trial CA209-067, for the comparison of nivolumab monotherapy and ipilimumab monotherapy, and some additional data was available in a paper by Larkin et al (NEJM, 31 May 2015). The PSCR also presented an indirect comparison of nivolumab (CA209-067) and pembrolizumab (KN-006) using ipilimumab as the common reference.

- 6.50 The submission stated that, given the financial expenditure predicted, the sponsor expected that there would be a need for a Deed of Agreement. The proposed Special Pricing Arrangement (SPA) had two components:
- Published versus effective price with a rebate proposed to accommodate the difference.
 - The submission stated it is impossible for the sponsor to provide detailed proposals for a capped arrangement until the restriction, price and base case estimates are agreed. The submission indicated one proposed structure that may be discussed includes a capped approach that manages any residual risk associated with inappropriate expenditure. While sharing the risk of use of nivolumab outside of both the initial and continuing restrictions was important, consideration of the substantial overestimate of the net cost to Government was also required.

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

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend nivolumab for the treatment of unresectable or metastatic (Stage III or IV) melanoma. In reaching this conclusion, the PBAC did not accept that ipilimumab, as presented in the submission, was the appropriate comparator.
- 7.2 The PBAC noted that the TGA had not completed its review of nivolumab at the time of PBAC consideration.
- 7.3 Following its recommendation of pembrolizumab through a managed entry scheme (MES) at its March 2015 meeting, the PBAC considered that pembrolizumab was the appropriate comparator. It is also a PD-1 inhibitor, so it is in the same pharmacological class as nivolumab. Further, the proposed patient population for nivolumab would receive pembrolizumab following its PBS listing in September 2015. For both these reasons, pembrolizumab was considered the appropriate comparator.
- 7.4 The PBAC agreed with the ESC that the indirect comparison between nivolumab and ipilimumab presented in the submission was unreliable due to poor exchangeability of the trials. The PBAC noted that CA209-067 would likely provide stronger support for the submission's clinical claim of superior comparative efficacy and safety over ipilimumab, but noted that the information about this trial and its results were limited and still emerging. The PBAC also considered that the extent of superior comparative effectiveness and safety of nivolumab compared with ipilimumab had not been adequately established by the submission and, due to several issues with the economic model, the resulting ICER was highly uncertain.
- 7.5 The PBAC considered that the incremental cost per QALY of nivolumab over ipilimumab presented in the submission's base case analysis, \$45,000 - \$75,000, was significantly underestimated and did not accurately represent the cost-effectiveness of nivolumab over ipilimumab due to the following concerns with the economic model:

- The unnecessarily complex approach to modelling the transitions across the usual three health state structure of a model in metastatic cancer resulted in counter-intuitive results when tested in sensitivity analyses which could not be readily explained.
- The lack of sensitivity analyses employing alternative curves to the log-logistic extrapolation method. In addition, the model did not use Kaplan-Meier trial-based data followed by extrapolated curves, and instead used solely modelled curves. The PBAC noted its preference for economic evaluations that directly reflect the trial data before using modelling to extrapolate beyond the median duration of follow-up in the trials.
- The 10-year time horizon is not strongly supported by the clinical evidence and favoured nivolumab significantly in the economic model.
- 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 extrapolations used in the model were based on treatment effects which were derived from an indirect comparison of poorly exchangeable trials that was likely to be biased, in favour of nivolumab (healthier trial patients).
- 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 have a significant effect on the ICER.
- The model assumed no further lines of therapy and did not incorporate costs of patients continuing nivolumab treatment beyond progression, which would be likely to occur in clinical practice.
- Adverse events were not included in the model.

7.6 The PBAC considered that the indirect comparison of nivolumab and pembrolizumab presented in the PSCR, based on CA209-067 and KN-006 with ipilimumab as the common reference, suggested that they may be similar, however limited information was available to assess the exchangeability of these two trials, including whether the duration of follow-up was similar across the data analysed from the two trials. The possible signal of reduced colitis was considered in the light of emerging Australian evidence that colitis may have been under-reported in the ipilimumab trials, and so the extent of colitis following any of these recent cancer immunotherapies in regular clinical practice is not yet known with confidence. Given the risk-share arrangements applying to pembrolizumab as part of its MES (an option rejected by the sponsor of nivolumab), nivolumab would not be cheaper, and its fortnightly dosing regimen is less convenient than pembrolizumab's dosing regimen of every three weeks.

7.7 In comparing the strength of the evidence available for the two PD-1 inhibitors, the PBAC recalled that, by the time of its March 2015 consideration of pembrolizumab, the early results of KN-006 were made available, and showed a statistically significant prolongation in median progression-free survival of pembrolizumab compared with ipilimumab based on the RECIST criteria, which the PBAC had considered was likely to be clinically meaningful. The PBAC noted that CA209-067 was yet to report on outcomes to this extent. The PBAC also noted that CA209-067 was primarily a comparison of nivolumab and ipilimumab combination therapy with nivolumab monotherapy and with ipilimumab monotherapy rather than comparing the two monotherapies. Further, CA209-067 was still ongoing, and data on overall

survival was still being collected, whereas data collection for KN-006 was stopped between March and July 2015 following an interim analysis.

- 7.8 The PBAC considered that, due to the various issues with the model and inappropriate choice of comparator, any resubmission should be a major submission to allow for evaluation.
- 7.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor continues to work with the PBAC to ensure nivolumab is available to Australian patients via the PBS in the earliest possible timeframe.