

7.06 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 The resubmission requested a Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required listing for the concurrent use of nivolumab and ipilimumab for the treatment of unresectable Stage III or Stage IV malignant melanoma. The first submission was considered by the PBAC in November 2015.

2 Requested listing

- 2.1 The requested restriction, including both induction (combination nivolumab and ipilimumab) and continuing (single-agent nivolumab) treatment phases, is provided below. The ESC's suggestions are in italics, with deletions in strikethrough, noting that further changes would be necessary to create separate restrictions for nivolumab and ipilimumab.

2.2

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
NIVOLUMAB 40 mg/4 mL injection, 1 x 4 mL vial 100 mg/10 mL injection, 1 x 10 mL vial	120 mg	3	\$ [REDACTED] (private) \$ [REDACTED] (public)	Opdivo® Squibb Australia Pty Ltd (BQ)
IPILIMUMAB 200 mg/40 mL injection, 1 x 40 mL vial 50 mg/10 mL injection, 1 x 10 mL vial	360 mg	3	\$ [REDACTED] (private) \$ [REDACTED] (public)	Yervoy® Squibb Australia Pty Ltd (BQ)

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:	Induction (combination nivolumab and ipilimumab) phase
Restriction Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must be receiving PBS-subsidised nivolumab and ipilimumab concomitantly for this condition, AND Patient must not have received prior treatment with ipilimumab or a PD-1 inhibitor, AND The treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks, the treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
NIVOLUMAB 40 mg/4 mL injection, 1 x 4 mL vial 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	11	\$ [REDACTED] (private) \$ [REDACTED] (public)	Opdivo® Squibb Australia Pty Ltd (BQ)

Treatment phase:	Continuing (single-agent nivolumab) phase
Restriction Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescriptions for <i>induction phase ipilimumab and nivolumab combination therapy</i> this drug for this condition, AND <i>This drug must be the sole PBS-subsidised treatment for this condition,</i> AND Patient must have stable or responding disease, AND The treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks.
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

- 2.2 The requested restriction differed from current listings for programmed death 1 (PD-1) inhibitors for melanoma with regard to the following criteria:
- induction (combination) phase
- patients with BRAF V600 mutation positive melanoma were not required to have progressed following BRAF inhibitor treatment;
 - the listing did not state that patients must not have received prior treatment with a PD-1 inhibitor for this condition;
 - there was no administrative note regarding the possibility of early 'pseudo-progression'; and
- continuing (single-agent) phase
- the listing did not state that the treatment must be the sole PBS-subsidised therapy for this condition.
- 2.3 The PSCR acknowledged that eligibility for nivolumab in combination with ipilimumab (NIVO+IPI) in patients with BRAF mutant melanoma should be restricted to those who have progressed following treatment with a BRAF inhibitor, consistent with the current listing for nivolumab in melanoma. The ESC, however, noted that there were no clinical data to support the use of NIVO+IPI in the second-line setting following a BRAF inhibitor, nor was this strategy included in the economic model presented in the resubmission. The ESC therefore advised that any PBS listing should be restricted to patients with BRAF wild type melanoma only.
- 2.4 The ESC suggested that the induction phase listing for nivolumab should restrict use to patients who have not received prior treatment with a PD-1 inhibitor, as there was no evidence to support the use of NIVO+IPI combination therapy following prior PD-1 inhibitor therapy. It is also suggested that the continuation phase restriction should specify that the patient must have previously been issued with an authority prescription for concomitant use of nivolumab with ipilimumab, to prevent use of this item number following initial treatment with nivolumab monotherapy.
- 2.5 The pre-PBAC response proposed that NIVO+IPI be used in the second-line setting after a BRAF-inhibitor for BRAF-mutant patients, and that NIVO+IPI has proven activity in BRAF-mutant patients, and restricting access to patients with BRAF wild type melanoma would be inappropriate.
- 2.6 The PBAC noted the findings of a recent network meta-analysis on immune checkpoint inhibitors and targeted therapies for metastatic melanoma (Pasquali et al, 2017) which showed that a combination of BRAF+MEK inhibitors was both more efficacious and less toxic than combination immunotherapy.*
- 2.7 The resubmission sought listing based on a cost-utility analysis of NIVO+IPI followed by best supportive care (BSC) upon disease progression compared with nivolumab monotherapy followed by ipilimumab monotherapy upon disease progression.

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

* Pasquali, S. et al. (2017). Immune checkpoint inhibitors and targeted therapies for metastatic melanoma: A network meta-analysis, *Cancer Treatment Reviews* 54:34-42

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Nivolumab, in combination with ipilimumab, was registered by the TGA and listed in the Australian Register of Therapeutic Goods on 11 January 2016 for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH)[†]. The requested PBS restriction was broader than the TGA-approved indication by including patients with unresectable Stage III disease and not restricting the use of NIVO+IPI combination therapy to patients with M1c disease or elevated LDH.
- 3.2 While acknowledging the increased toxicity associated with combination therapy, the Advisory Committee on Prescription Medicines (ACPM) was of the view that combination therapy has a role in the treatment of patients with poor prognosis who generally do not respond well on treatment with ipilimumab or nivolumab monotherapy. This poor prognosis group can be identified by elevated LDH or M1c melanoma (ACPM ratified minutes of meeting 307, 3-4 December 2015). No further details were provided for the ACPM decision. The ESC advised that the PBAC may wish to further restrict any PBS listing to patients with M1c melanoma or elevated LDH levels, in line with the TGA-approved indication. The PSCR stated that, in CA209-067, 209/214 (66.6%) of NIVO+IPI patients and 204/316 (64.6%) of nivolumab patients had M1c melanoma or elevated LDH levels.
- 3.3 The resubmission stated that an application to the TGA was planned for the end of 2016 or early 2017, with the purpose of broadening the TGA indication to include all patients with unresectable or metastatic melanoma, irrespective of metastatic (M) stage, thereby matching the key clinical trial population.
- 3.4 This was the second consideration of NIVO+IPI by the PBAC for the treatment of unresectable Stage III or Stage IV malignant melanoma. Pembrolizumab and nivolumab, two PD-1 inhibitors, were recommended as monotherapies by the PBAC in March 2015 and November 2015, respectively, for the same indication. Ipilimumab was recommended by the PBAC in November 2012 for this indication. In July 2016, the PBAC recommended an amendment to the restriction wording for the PBS listing of ipilimumab for this indication from “the treatment must be as monotherapy” to “the treatment must be the sole PBS-subsidised therapy for this condition.”
- 3.5 The previous submission nominated ipilimumab monotherapy as the main comparator. This was revised to pembrolizumab monotherapy in the Pre-Subcommittee Response following that submission. The main comparator nominated in the resubmission was sequential PD-1 inhibitor monotherapy followed by ipilimumab monotherapy upon disease progression, and new economic and financial analyses were provided. The key differences between the previous submission and the current resubmission are summarised below.

[†] Metastatic (M) classification of melanoma: M0 – no distant metastasis; M1a – distant skin, subcutaneous, or nodal metastases, normal LDH; M1b – lung metastases, normal LDH; M1c – all other viscera metastases with normal LDH or any distant metastases with elevated LDH. The presence of distant metastases (M stage) and elevated LDH level are both negative prognostic factors in cutaneous melanoma.

Table 1: Summary of the key differences between the previous submission and current resubmission

	Submission considered in November 2015	Current resubmission
Main comparator	<p>The submission nominated ipilimumab monotherapy. Revised to pembrolizumab monotherapy in the PSCR. Additional comparator: nivolumab monotherapy.</p> <p>PBAC Comment: The PBAC considered that the revised main comparator, pembrolizumab monotherapy, was appropriate, but considered that sequential use of a PD-1 inhibitor followed by ipilimumab, and dabrafenib ± trametinib were also appropriate comparators (paragraph 7.3, November 2015 PSD).</p>	<p>Sequential use of PD-1 inhibitor monotherapy followed by ipilimumab monotherapy upon progression. An additional comparison with dabrafenib ± trametinib was been provided, even though the requested listing does not preclude the treatment of BRAF mutant melanoma.</p>
Clinical evidence	<p>Direct comparisons of NIVO+IPI combination therapy with ipilimumab monotherapy and nivolumab monotherapy (Trials CA209-067 and CA209-069) Indirect comparison of combination therapy with pembrolizumab monotherapy.</p>	<p>Direct comparison of NIVO+IPI combination therapy with nivolumab monotherapy in the first-line setting (CA209-067).</p>
Key effectiveness data*	<p>PFS: NIVO+IPI vs NIVO monotherapy HR 0.74 (95% CI: 0.60, 0.92) Difference in median PFS 4.6 months OS data not available.</p>	<p>NIVO+IPI versus NIVO monotherapy: PFS: HR 0.76 (95% CI: 0.62, 0.94) Difference in median PFS 4.8 months OS: HR 0.88 (95% CI: 0.69, 1.12) Median OS not reached in either treatment arm.</p>
Economic model	<p>Cost-utility model with cost/QALY: NIVO+IPI vs NIVO: \$45,000 - \$75,000/QALY gained</p>	<p>Cost-utility model with a dominant ICER. There was an error in the resubmission's model which, when corrected, resulted in an ICER of more than \$200,000/QALY. The PSCR accepted this error (& other modifications) to result in an ICER of more than \$200,000/QALY gained.</p>
Financial analysis	<p>The incidence of unresectable Stage III and Stage IV malignant melanoma was based on projections of mortality rates from AIWH data and the 12-month survival rate for ipilimumab. The treatment algorithms and the assumed uptake of alternative treatments were based on expert opinion. Less than 10,000 patients in Year 1 increasing to less than 10,000 in Year 5. \$30 - \$60 million in Year 1 increasing to \$30 - 60 million in Year 5 for a total of more than \$100 million over the first 5 years of listing.</p>	<p>New analysis presented reflecting the change in comparator. Incidence based on 2014 PBS data from the DUSC report 'Ipilimumab and dabrafenib: predicted versus actual analysis.' The proposed treatment algorithms and the assumed uptake of alternative treatment options were based on expert opinion but differed from the previous submission. 750 patients in Year 1 increasing to 800 in Year 5. \$30 - \$60 million in Year 1 increasing to \$30 - \$60 million in Year 5 for a total of more than \$100 million over the first 5 years of listing.</p>
PBAC decision	<p>Reject. 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 (paragraph 7.1, November 2015 PSD).</p>	-

CI = confidence interval; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PD-1 = programmed death 1; PFS = progression-free survival; PSCR = Pre-subcommittee response; PSD = Public Summary Document; QALY = quality-adjusted life-year

* Only data relevant to the comparison of NIVO+IPI versus nivolumab monotherapy have been summarised from the November 2015 submission.

Source: Compiled during the evaluation

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

4 Clinical place for the proposed therapy

- 4.1 Nivolumab is a human monoclonal immunoglobulin G4 antibody that acts as a PD-1 immune checkpoint inhibitor. Ipilimumab is a recombinant human monoclonal antibody that selectively binds to cytotoxic T lymphocyte associated antigen 4 (CTLA-4). The two agents target two distinct checkpoint pathways. PD-1 inhibitors reactivate T-cells at the tumour site and CTLA-4 inhibitors increase the number of activated T-cells migrating to the tumour.
- 4.2 The resubmission considered that NIVO+IPI would be used in the first-line setting for patients with BRAF wild type melanoma, while the vast majority of patients with BRAF mutant melanoma would receive first-line BRAF inhibitor treatment followed by second-line NIVO+IPI upon progression. However, the requested restriction included all patients with stage III or IV unresectable metastatic melanoma, irrespective of BRAF status or treatment line. This was unchanged from the previous submission. Under the requested restriction, NIVO+IPI may substitute for the combination of BRAF and MEK inhibitors in the first-line setting. No comparative evidence was provided to support the use of NIVO+IPI in place of the combination of a BRAF and MEK inhibitor in the first-line setting. Similarly, no evidence was provided to support the use of NIVO+IPI in the second-line setting following a BRAF/MEK inhibitor.

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

5 Comparator

- 5.1 The resubmission nominated the treatment sequence of PD-1 inhibitor monotherapy followed by ipilimumab monotherapy upon disease progression (in the first/second-line setting for patients with BRAF wild type melanoma and in the second/third-line setting post first-line BRAF/MEK inhibitor in patients with BRAF mutant melanoma) as the main comparator for NIVO+IPI combination therapy.
- 5.2 The PBAC previously considered that the revised main comparator in the November 2015 submission, pembrolizumab monotherapy, was appropriate, and that the sequential use of a PD-1 inhibitor followed by ipilimumab, and dabrafenib ± trametinib for BRAF mutant patients, were also appropriate comparators (paragraph 7.3, 5.10 nivolumab plus ipilimumab Public Summary Document (PSD), November 2015 PBAC meeting). Nivolumab, as monotherapy, was not listed for this indication at the time of the previous submission. The resubmission stated that it chose not to compare NIVO+IPI combination with PD-1 inhibitor monotherapy, as substitution for such would be relatively minor compared to substitution for the two monotherapies in sequence. This claim was poorly supported as it was based on expert opinion (n=7).

- 5.3 The PSCR stated that the comparator selection was guided by an advisory board of seven clinical advisors (who treat approximately 50% of metastatic melanoma patients in Australia). The board stated that combination therapy would replace sequential therapy if PBS listed. The ESC advised that the current PBS data shows that the majority of patients who are currently being treated with ipilimumab have previously received treatment with a PD-L1 inhibitor.
- 5.4 Since the nominated comparator spans two treatment lines, the requested treatment regimen should also span two treatment lines. The resubmission's economic model was based on a comparison of the following two treatment strategies:
- first-line NIVO+IPI followed by BSC upon disease progression, and
 - first-line nivolumab monotherapy followed by ipilimumab monotherapy upon disease progression.
- 5.5 The resubmission appeared to define BSC as the absence of any systemic anti-cancer therapy. Assuming no patients would receive further systemic therapy following progression on NIVO+IPI was not consistent with:
- the proposed treatment algorithm presented in Section A, which indicated that, of those who progress on NIVO+IPI, 25% of patients with BRAF wild type melanoma and approximately 20% of patients with BRAF mutant melanoma would receive chemotherapy; and
 - the key trial presented in Section B of the resubmission (CA209-067), in which 32% of all randomised patients in the NIVO+IPI treatment arm had received subsequent systemic therapy at the latest database lock in September 2016 (only 54% of patients in the NIVO+IPI arm had experienced a progression event at this time-point).
- 5.6 Furthermore, the current listing for ipilimumab allows for re-induction of treatment in patients who have progressive disease after achieving an initial objective response, therefore subsequent treatment with ipilimumab monotherapy may occur following progression on either NIVO+IPI or nivolumab monotherapy.
- 5.7 The pre-PBAC response stated that the pivotal trial CA209-067 did not allow NIVO+IPI patients to be retreated with IPI and the sponsor maintained that retreatment with IPI should not be permitted under the PBS listing.

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 (1), health care professionals (2), and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the substantial, rapid and durable clinical

benefits observed using nivolumab and ipilimumab combination therapy. In addition, the comments emphasised the severity of adverse events associated with combination therapy, noting the intensive involvement of the healthcare team in monitoring for and managing these adverse events. It was also noted that patients who discontinue due to toxicity may also experience the most durable responses to therapy.

- 6.3 The PBAC noted the correspondence received from the Australian Melanoma Consumer Alliance supporting equitable access to NIVO+IPI combination therapy as a “life-prolonging” option for patients with advanced melanoma. The PBAC also noted the advice from Melanoma Patients Australia (MPA), expressing support for the listing. MPA also provided a summary of individual patient comments, describing the benefits of treatment response, the severity of AEs, and the acceptability of this benefit-harm profile.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the NIVO+IPI submission, on the basis of being supported by phase 3 trial evidence. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for NIVO+IPI, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[‡], based on a comparison with ipilimumab.
- 6.5 The PBAC noted the advice prepared by an expert clinician and forwarded by the sponsor, clarifying the likely use of NIVO+IPI in clinical practice. The PBAC specifically noted the advice that the use of NIVO+IPI was of particular benefit in patients with rapidly progressing disease, who benefit from the higher response rates associated with combination immunotherapy. These patients include patients with BRAF mutant melanoma who may progress rapidly following cessation of first-line BRAF+MEK inhibitor treatment. The clinician emphasised that AEs could be managed by experienced clinicians with careful patient selection and early intervention, and that the majority could be managed without hospital admission. The PBAC noted that this advice was consistent with the evidence provided in the submission.

Clinical trials

- 6.6 No direct randomised trials were identified that compared NIVO+IPI followed by BSC upon progression versus PD-1 inhibitor monotherapy followed by ipilimumab monotherapy upon progression. Therefore, the resubmission used a strategy of separating out the lines of therapy (see Figure 1 below).
- 6.7 The resubmission was based on the following trials in patients with unresectable Stage III or Stage IV malignant melanoma:
- CA209-067: a randomised, double-blind, three-arm trial comparing NIVO+IPI and nivolumab monotherapy to ipilimumab monotherapy in previously untreated patients (n=945). This trial was also presented as key evidence in the previous submission. Updated results were provided in the resubmission.

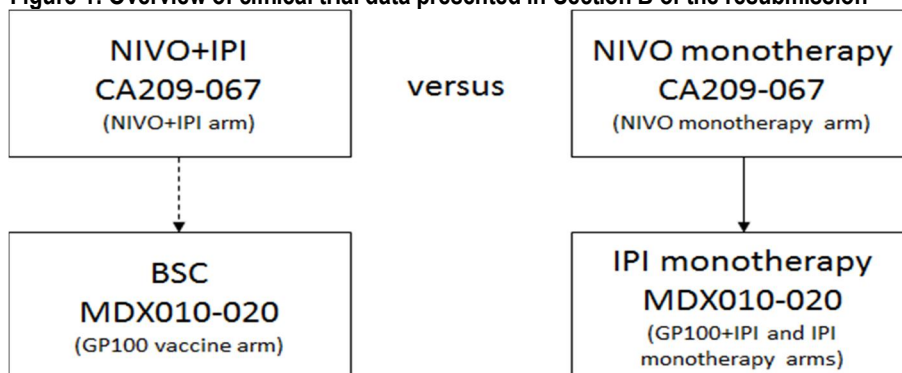
[‡] Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 26:1547-73, 2015

- MDX010-020: a randomised, double-blind, three-arm trial comparing ipilimumab monotherapy, melanoma peptide vaccine gp100 and combination ipilimumab+gp100 in patients who had relapsed, failed, or were not able to tolerate at least one or more prior treatment regimens.

Neither trial restricted eligibility for treatment by BRAF mutation status.

6.8 The approach taken in the submission is summarised in Figure 1.

Figure 1: Overview of clinical trial data presented in Section B of the resubmission



BSC = best supportive care; IPI = ipilimumab; NIVO= nivolumab

Note: The dashed arrow indicates the implicit assumption in the resubmission that patients will only receive BSC following progression on NIVO+IPI.

Source: Constructed during the evaluation, adapted from Figure 10, p45 of the resubmission.

6.9 Details of the trials presented in the resubmission are provided in the table below.

Table 2: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
CA209-067	Interim Clinical Study Report: 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. Database lock February 2015. Topline Report. Database lock September 2016. Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma	19 June 2015 18 October 2016 <i>NEJM</i> 2015; 373 (1): 23-34.
MDX010-020	Clinical Study Report: A randomized, double-blind, multicentre 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. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma.	May 2010 <i>NEJM</i> 2010; 363 (8): 711-23.

Source: Table 16, p53 and Table 19, p56 of the resubmission.

6.10 The key features of the randomised trials are summarised in the table below.

Table 3: Summary of trials presented in the resubmission

Trial ID	N	Comparison	Trial design	Outcomes	Use in the economic evaluation
NIVO+IPI versus nivolumab monotherapy – first line					
CA209-067	945	- NIVO 1mg/kg IV, plus IPI 3mg/kg, Q3W x 4, then NIVO 3mg/kg IV Q2W (n=314) - NIVO 3mg/kg IV Q2W (n=316) - IPI 3mg/kg IV Q3W x 4 (n=315)	Phase III R, DB, MC	PFS, OS	Transition from: P0 → P1 P0 → Death
BSC versus ipilimumab monotherapy – second line*					
MDX010-020	676	- IPI 3mg/kg IV Q3W plus gp100 SC Q3W ^a , up to 4 doses ^b (n=403) - IPI 3mg/kg IV Q3W, up to 4 doses ^b (n=137) - gp100 SC Q3W ^a , up to 4 doses ^b (n=136)	Phase III R, DB, MC	PFS, OS	Transition from: P1 → P2 P1 → Death P2 → Death

BSC = best supportive care; DB = double blind; IPI = ipilimumab; IV = intravenous; MC = multi-centre; NIVO = nivolumab; OS = overall survival; P0 = alive, no progression health state; P1 = alive post 1st progression; P2 = alive post 2nd progression; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; R = randomised; SC = subcutaneous

^a The melanoma peptide vaccine gp100 contained 2 mg Peptide A and 2 mg Peptide B.

^b Patients with stable disease for 3 months' duration after week 12 or a confirmed partial or complete response could receive additional courses of therapy with their assigned treatment regimen if they had disease progression.[§]

* Patients in MDX010-020 must have previously received at least one course of systemic treatment. Prior therapies included interleukin-2, dacarbazine, temozolamide, fotemustine and/or carboplatin.

Source: Compiled during the evaluation

- 6.11 CA209-067 provided clinical evidence for the comparative effectiveness and safety of NIVO+IPI relative to nivolumab monotherapy in the first-line setting, with a variety of subsequent therapies used in both treatment arms. Of patients who had experienced a progression event (documented progression or death) at the September 2016 database lock, approximately 60% in the NIVO+IPI arm and 70% in the nivolumab monotherapy arm had received at least one subsequent systemic therapy. Of the patients in the nivolumab monotherapy arm who received further systemic therapy, 59% had received ipilimumab.
- 6.12 The use of BRAF inhibitors and PD-1 inhibitors post-progression in the trial did not reflect the current PBS listings for these drugs. These are precluded in patients who have received prior treatment with a PD-1 inhibitor.
- 6.13 MDX010-020 did not provide clinical evidence directly relevant to the nominated comparison of NIVO+IPI followed by BSC versus PD-1 inhibitor monotherapy followed by ipilimumab monotherapy. The resubmission used MDX010-020 to provide data specific to the comparison of BSC with ipilimumab monotherapy in the second-line setting, using the gp100 treatment arm as a surrogate for BSC. None of the patients in MDX010-020 were reported to have received a prior PD-1 inhibitor. Therefore, the trial population was not representative of the population who have progressed after treatment with NIVO+IPI or nivolumab monotherapy.
- 6.14 The progression-free survival (PFS) and overall survival (OS) results from MDX010-020 were used in the economic evaluation to model transitions from the P1 health

[§] Hodi FS, O'Day SJ, *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010; 363 (8):711-23

state (alive after first progression) to the P2 health state (alive after second progression) and from P1 and P2 to the “dead” health state.

Comparative effectiveness

- 6.15 The OS results from the CA209-067 September 2016 database lock (28 months minimum follow-up) are summarised in Table 4 below. The corresponding Kaplan-Meier plot is presented in Figure 2.

Table 4: Overall survival results in patients with BRAF WT and MT tumours, CA209-067 minimum follow-up 28 months

	NIVO+IPI N=314	Nivolumab monotherapy N=316
Number of events, n (%)	128 (40.8%)	142 (44.9%)
Median OS, months (95% CI)	NA	NA (29.1, NA)
Stratified HR (95% CI) ^{a, b}	0.88 (0.69, 1.12)	
OS rate, % (95% CI)		
OS rate at 12 months	73% (68%, 78%)	74% (69%, 79%)
OS rate at 18 months	68% (62%, 73%)	65% (60%, 70%)
OS rate at 24 months	64% (59%, 69%)	59% (53%, 64%)

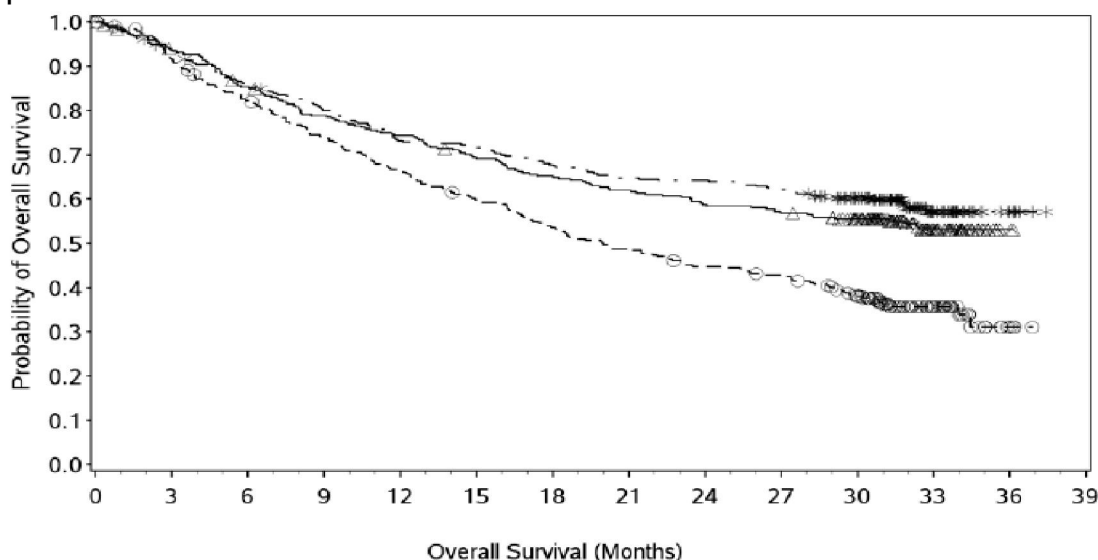
CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; MT = mutant type; NA = not available; NIVO = nivolumab; OS = overall survival; WT = wild type

^a NIVO+IPI versus nivolumab monotherapy

^b Stratified by PD-L1 status, BRAF status and M stage.

Source: Table 31, p85 and Table 32, p86 of the resubmission and Table 3.3.1-1, p7 Topline Report database lock September 2016, Attachment 6 to the resubmission.

Figure 2: Kaplan Meier plot for OS in patients with *BRAF* WT and MT tumours, CA209-067 minimum follow-up 28 months



Number of Subjects at Risk														
	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Nivolumab	316	292	265	244	230	213	201	191	181	175	157	55	3	0
Nivolumab + Ipilimumab	314	292	265	247	226	221	209	200	198	192	170	49	7	0
Ipilimumab	315	285	254	228	205	182	164	149	136	129	104	34	4	0

—△— Nivolumab (events: 142/316), median and 95% CI: N.A. (29.08, N.A.)
 - - -●- - Nivolumab + Ipilimumab (events: 128/314), median and 95% CI: N.A.
 - - -■- - Ipilimumab (events: 197/315), median and 95% CI: 19.98 (17.08, 24.61)

Nivolumab vs Ipilimumab - hazard ratio and 98% CI: 0.63 (0.48, 0.81); p-value: <0.0001
 Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 98% CI: 0.55 (0.42, 0.72); p-value: <0.0001
 Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.88 (0.69, 1.12)

CI = confidence interval; MT = mutant type; NA = not available; WT = wild type
 Source: Figure 12, p85 of the resubmission.

- 6.16 The resubmission stated that the Kaplan-Meier OS analysis descriptively showed an improvement favouring NIVO+IPI over nivolumab monotherapy, and that the incremental difference between the NIVO+IPI survival rate and the nivolumab monotherapy survival rate was widening over time (favouring NIVO+IPI). The OS results were immature.
- 6.17 After a minimum follow-up of 28 months, the hazard ratio (HR) for OS for NIVO+IPI vs nivolumab monotherapy was 0.88 (95% confidence interval (CI): 0.69, 1.12). The median OS had not been reached in either the NIVO+IPI or the nivolumab monotherapy treatment arms.
- There was no statistically significant difference in OS between the two treatment arms, although it should be noted that the comparison of NIVO+IPI and nivolumab monotherapy was only a secondary objective and the trial was not adequately powered for this comparison. The PSCR stated that future data cuts (3-year OS) are projected to be presented in September 2017.
 - There was no difference in OS between the two treatment arms over the first 12 months following randomisation, with a 5% difference in OS at 24 months.

6.18 Table 5 below compares the PFS results presented in the previous submission (February 2015 database lock) with the updated results from the September 2016 database lock. The Kaplan-Meier curves for PFS, based on the updated data, are presented in Figure 3.

Table 5: Progression-free survival results in patients with *BRAF* WT and MT tumours, CA209-067

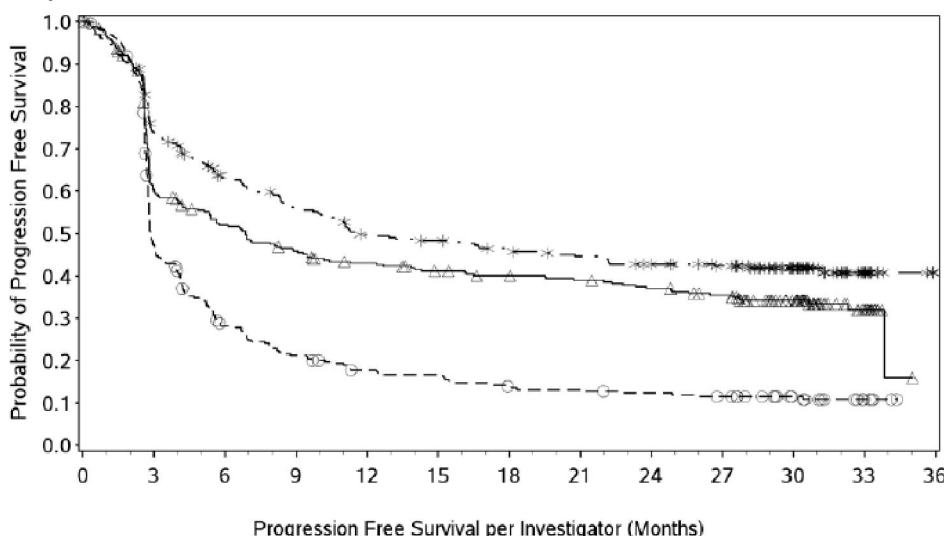
	CA209-067 CSR Minimum follow-up 9 months		CA209-067 Topline report Minimum follow-up 28 months	
	NIVO+IPI N=314	NIVO mono N=316	NIVO+IPI N=314	NIVO mono N=316
Number of events, n (%)	151 (48.1%)	174 (55.1%)	169 (53.8%)	195 (61.7%)
Median PFS, months (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	11.7 (8.9, 21.9)	6.9 (4.3, 9.5)
Direct HR (95% CI) ^a	0.74 (0.60, 0.92)		0.76 (0.62, 0.94)	

CI = confidence interval; CSR = Clinical study report; HR = hazard ratio; IPI = ipilimumab; mono = monotherapy; MT = mutant type; NIVO = nivolumab; PFS = progression-free survival; WT = wild type

^a NIVO+IPI versus nivolumab monotherapy

Source: Table 33, p88 of the resubmission

Figure 3: Kaplan Meier plot for PFS in patients with *BRAF* WT and MT tumours, CA209-067 minimum follow-up 28 months



Number of Subjects at Risk													
Nivolumab	316	178	151	132	120	112	107	103	97	88	62	16	0
Nivolumab + Ipilimumab	314	218	176	156	137	132	125	118	110	104	71	16	0
Ipilimumab	315	136	77	58	46	43	35	33	30	27	16	5	0

—△— Nivolumab (events: 195/316), median and 95% CI: 6.87 (4.34, 9.46)
 - - - × - - - Nivolumab + Ipilimumab (events: 169/314), median and 95% CI: 11.73 (8.90, 21.88)
 . . . ○ . . . Ipilimumab (events: 253/315), median and 95% CI: 2.86 (2.79, 3.15)

Nivolumab vs Ipilimumab - hazard ratio and 95% CI: 0.54 (0.45, 0.66)
 Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 95% CI: 0.42 (0.34, 0.51)
 Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.76 (0.62, 0.94)

CI = confidence interval; MT = mutant type; PFS = progression-free survival; WT = wild type

Source: Figure 15, p88 of the resubmission.

6.19 The median PFS was 11.7 months in the NIVO+IPI arm, compared to 6.9 months in the nivolumab monotherapy arm. The PBAC previously noted that the combination therapy showed an improvement in median PFS of 4.6 months compared to

nivolumab monotherapy in the trial CA209-067, and considered that 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 resubmission has not addressed these concerns. The ESC noted that the PSCR did not address these concerns.

- 6.20 One of the secondary objectives of CA209-067 was to evaluate whether PD-L1 expression is a predictive marker for the effect of treatment on OS. Despite this, the resubmission did not report OS results categorised by PD-L1 status, nor did it provide updated subgroup analyses for PFS. The subgroup analyses of PFS by PD-L1 status, as presented in the previous submission, suggested that the addition of ipilimumab to first-line nivolumab therapy had minimal benefit in terms of PFS in PD-L1 positive patients ($\geq 5\%$ expression in tumour tissue). Although the analysis was exploratory and statistically underpowered, the HR for PFS in PD-L1 positive patients was close to one (HR 0.96; 95% CI: 0.58, 1.58), compared to an HR of 0.70 (95% CI: 0.54, 0.91) in the PD-L1 negative subgroup. Given that the safety profile of NIVO+IPI is inferior to that of nivolumab monotherapy, overall survival data by PD-L1 status may be necessary to fully inform a decision on listing with or without PD-L1 eligibility criteria.
- 6.21 Addendum 01 to the Clinical Study Report for CA209-067, reporting the PD-L1 results of CA209-067 by PD-L1 expression status, was provided with the PSCR. In this context, the ESC noted the conclusions in Larkin et al. (2015), that “Among previously untreated patients with metastatic melanoma, nivolumab alone or combined with ipilimumab resulted in significantly longer progression-free survival than ipilimumab alone. In patients with PD-L1–negative tumours, the combination of PD-1 and CTLA-4 blockade was more effective than either agent alone”. The ESC also noted that no request had been made to enrich the eligible population for the combination therapy according to PD-L1 expression status.

Comparative harms

- 6.22 The resubmission did not present any updated safety data from CA209-067. The safety outcomes in CA209-067 are summarised in Table 6 below.

Table 6: Summary of safety outcomes in CA209-067, minimum follow-up 9 months^a

Adverse event	NIVO+IPI	Monotherapy	RD (95% CI)	RR (95% CI)
NIVO+IPI vs NIVO monotherapy	NIVO+IPI N=313	Nivolumab N=313		
Overall drug-related AEs				
Any AE	299 (95.5%)	257 (82.1%)	0.13 (0.09, 0.18)	1.16 (1.10, 1.23)
Any serious AE	150 (47.9%)	25 (8.0%)	0.40 (0.34, 0.46)	6.00 (4.05, 8.89)
Any severe AE (Grade ≥3)	172 (55.0%)	51 (16.3%)	0.39 (0.32, 0.46)	3.37 (2.57, 4.42)
AE leading to discontinuation	114 (36.4%)	24 (7.7%)	0.29 (0.23, 0.35)	4.75 (3.15, 7.17)
NIVO+IPI vs IPI monotherapy	NIVO+IPI N=313	Ipilimumab N=311		
Overall drug-related AEs				
Any AE	299 (95.5%)	269 (86.2%)	0.09 (0.05, 0.13)^b	1.10 (1.05, 1.16)^b
Any serious AE	150 (47.9%)	69 (22.2%)	0.26 (0.19, 0.33)^b	2.16 (1.70, 2.74)^b
Any severe AE (Grade ≥3)	172 (55.0%)	86 (27.7%)	0.27 (0.20, 0.35)^b	1.99 (1.62, 2.44)^b
AE leading to discontinuation	114 (36.4%)	46 (14.8%)	0.22 (0.15, 0.28)^b	2.46 (1.82, 3.34)^b

AE = adverse event; CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; RD = risk difference; RR = risk ratio

^a Median follow-up 12.2-12.5 months across arms

^b Figures calculated during the evaluation

Bolded figures indicate statistically significant differences

Source: Table 32, p111, Table 36, p124, Table 55, p159, Table 58, p164 November 2015 submission.

- 6.23 The PBAC previously considered that combination treatment with nivolumab and ipilimumab had 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 (AEs) with NIVO+IPI 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 AE over nivolumab monotherapy, and an odds ratio for discontinuations due to drug-related AEs 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 (paragraph 7.5, 5.10 nivolumab plus ipilimumab, November 2015 PBAC meeting).
- 6.24 The PSCR argued that the vast majority of grade 3/4 AEs were manageable using established algorithms involving immune-modulating agents and resolve within 4-5 weeks (Sznol 2016).^{**} The ESC also noted the evidence in the PSCR that NIVO+IPI combination patients who discontinued treatment due to AEs still derived a significant efficacy benefit (Schadendorf 2016).^{††}
- 6.25 The resubmission also presented the safety data from the ipilimumab monotherapy arm of MDX010-020 as an indication of the safety profile of second-line ipilimumab monotherapy after progression on first line treatment with PD-1 inhibitors. The population in the MDX010-020 was not representative of the population who have progressed after first-line PD-L1 inhibitors, as none of the patients in MDX010-020 were reported to have received a prior PD-inhibitor. In addition, as the resubmission only presented safety outcomes for the ipilimumab monotherapy arm of the trial, these data were essentially non-comparative.

^{**} Sznol M et al. Safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. ESMO 2016, poster 3434.

^{††} Schadendorf D et al. Efficacy and safety outcomes in patients with advanced melanoma (MEL) who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity. EADO 2016, presentation.

- 6.26 The resubmission claimed that, although the frequency and severity of AEs with NIVO+IPI combination were higher than with either nivolumab or ipilimumab monotherapy, they were similar when considering the context of the sequence of nivolumab monotherapy followed by ipilimumab monotherapy. The sequential toxicity across two lines of treatment (additive toxicity) is not equivalent to the combined toxicity observed when the two treatments are administered concomitantly (multiplicative toxicity).
- 6.27 The TGA delegate reported that there was a clear signal of a major increase in toxicity with the combined use of PD-1 inhibitors and ipilimumab. Pneumonitis, hepatitis, hypophysitis and similar potentially fatal AEs were all seen at a much higher frequency than with use of nivolumab or ipilimumab monotherapy. The delegate also noted the apparent need for intense clinical monitoring to diagnose and manage immune-mediated reactions at an early stage, in order to maintain the good record of reversibility and absence of fatal adverse drug reactions seen in the key clinical trial for combination therapy.

Benefits/harms

- 6.28 A summary of the comparative benefits and harms for NIVO+IPI versus nivolumab monotherapy in treatment naïve patients is presented in the table below. No evidence was provided to support a comparison between NIVO+IPI followed by BSC versus nivolumab monotherapy followed by ipilimumab monotherapy.

Table 7: Summary of comparative benefits and harms for NIVO+IPI and nivolumab monotherapy – CA209-067

Benefit – PFS (minimum follow-up 28 months)*						
	NIVO+IPI	NIVO	Absolute difference	HR (95% CI)		
Progressed	169/314 (53.8%)	195/316 (61.7%)	-	0.76 (0.62, 0.94)		
Median PFS (months)	11.7 (8.9, 21.9)	6.9 (4.3, 9.5)	4.8	-		
Benefit – OS (minimum follow-up 28 months)*						
Death	128/314 (40.8%)	142/316 (44.9%)	-	0.88 (0.69, 1.12)		
Median OS (months)	NA	NA (29.1, NA)	-	-		
Harms						
	NIVO+IPI	NIVO	RR (95% CI)	Event rate/100 patients**		RD (95% CI)
				NIVO+IPI	NIVO	
Study-drug related AEs (minimum follow-up 9 months)**						
Any severe AE (Grade ≥ 3)	172/313 (55.0%)	51/313 (16.3%)	3.37 (2.57, 4.42)	55	16.3	0.39 (0.32, 0.46)
AE leading to discontinuation	114/313 (36.4%)	24/313 (7.7%)	4.75 (3.15, 7.17)	36.4	7.7	0.29 (0.23, 0.35)

AE = adverse event; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NA = not available; NIVO = nivolumab; OS = overall survival; PFS = progression-free survival; RD = risk difference; RR = risk ratio.

* Minimum duration of follow-up 28 months; median duration of follow-up not reported.

** Minimum duration of follow-up 9 months; median duration of follow-up 12.2-12.5 months across arms

Source: Compiled during the evaluation

- 6.29 On the basis of the direct evidence presented in the resubmission, there would be approximately 4.8 months increase in median progression-free survival in patients treated with NIVO+IPI in comparison with nivolumab monotherapy in the first-line setting. There would be no improvement in overall survival between these two groups, although the OS data were immature and the trial was not adequately

powered for this comparison. For every 100 patients treated with NIVO+IPI in comparison to nivolumab monotherapy over a minimum duration of follow-up of 9 months:

- approximately 39 additional patients would experience a Grade 3 or higher treatment-related severe AE;
- approximately 29 additional patients would experience a treatment-related AE leading to discontinuation of treatment.

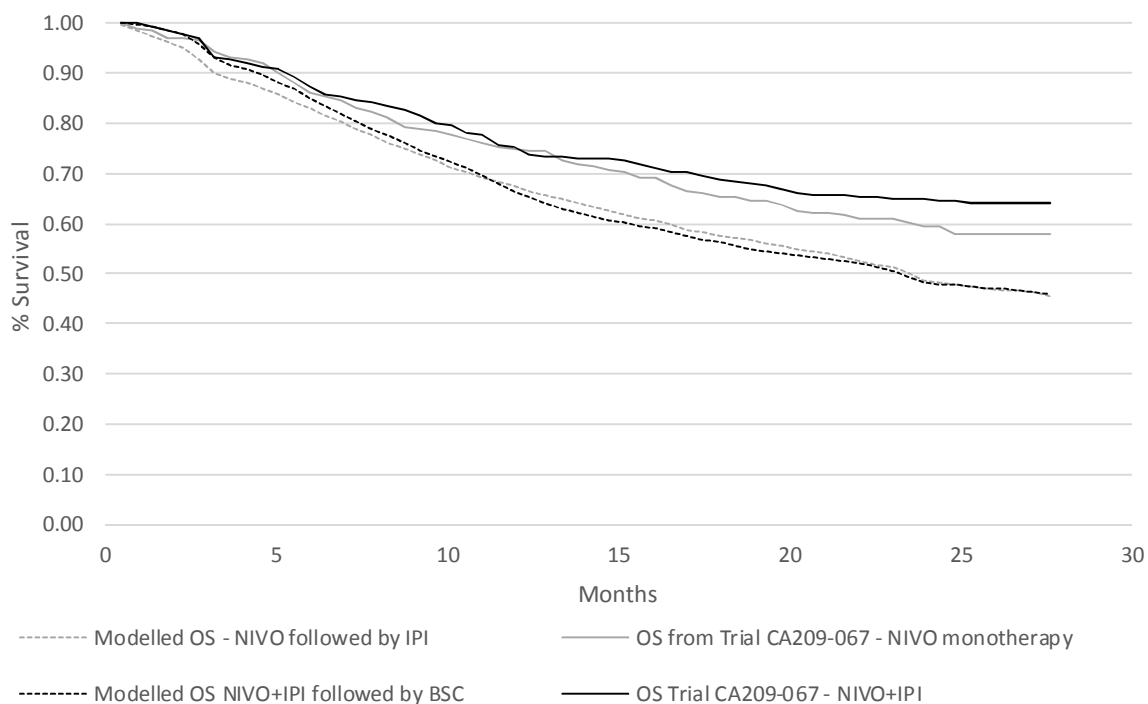
Clinical claim

- 6.30 The resubmission described NIVO+IPI combination therapy as superior in terms of comparative effectiveness and inferior in terms of comparative safety over sequential use of nivolumab monotherapy followed by ipilimumab monotherapy upon progression.
- 6.31 The claim of superior comparative effectiveness was not adequately supported. No evidence for the comparative safety and effectiveness of NIVO+IPI followed by BSC versus nivolumab followed by ipilimumab was provided in the resubmission.
- 6.32 Although the evidence on comparative safety did not include a direct comparison of NIVO+IPI followed by BSC versus nivolumab monotherapy followed by ipilimumab monotherapy, such evidence as was available did not contradict the sponsor's acknowledgement of inferior comparative safety.
- 6.33 CA209-067 provided evidence on the comparative effectiveness and safety of NIVO+IPI and nivolumab monotherapy in the first-line setting, with both trial arms followed by a variety of subsequent systemic therapies, in patients with Grade III/IV melanoma, unselected by BRAF status:
- there was no statistically significant difference in OS between the NIVO+IPI and the nivolumab monotherapy treatment arms, although the data were immature and the trial was not adequately powered for this comparison;
 - combination therapy with NIVO+IPI resulted in an improvement in median PFS of approximately 4.8 months compared with nivolumab monotherapy;
 - there were significantly higher rates of serious AEs with NIVO+IPI combination therapy compared to nivolumab monotherapy;
 - in the absence of conclusive evidence that first-line NIVO+IPI confers any benefit over first-line nivolumab monotherapy in terms of overall survival, the clinical significance of an improvement in PFS of 4.8 months should be considered against the considerable increase in toxicity associated with combination therapy.
- 6.34 The PBAC reiterated that the claim of superior comparative effectiveness was demonstrated for a gain in PFS, 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.
- 6.35 The PBAC reiterated that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.36 The resubmission presented a modelled economic analysis comparing two alternative treatment strategies:
- first-line NIVO+IPI followed by second-line BSC; and
 - first-line nivolumab followed by second-line ipilimumab.
- 6.37 The economic model presented in the resubmission used:
- Trial CA209-067 data to inform PFS and OS for first-line NIVO+IPI and first-line nivolumab monotherapy; and
 - unadjusted results from Trial MDX010-020 to inform PFS and OS for second-line BSC (gp100 vaccine arm) and second-line ipilimumab (combined gp100 vaccine + ipilimumab and ipilimumab monotherapy arms).
- 6.38 The model did not allow for active treatments following failure of first-line therapy in the NIVO+IPI arm and assumed that all patients who progress from first-line nivolumab monotherapy in the comparator arm will subsequently receive ipilimumab. This was not reasonable. Of patients who had experienced a progression event (documented progression or death) at the September 2016 database lock, approximately 60% in the NIVO+IPI arm had received at least one subsequent systemic therapy and 70% in the nivolumab monotherapy arm had received at least one subsequent systemic therapy. Of the patients in the nivolumab monotherapy arm who received further systemic therapy, 59% had received ipilimumab. The PSCR acknowledged that approximately 30-35% of patients receiving NIVO monotherapy may not be well enough to receive IPI therapy in the second-line setting. The model's assumptions therefore underestimate the cost associated with the NIVO+IPI arm and overestimate the costs associated with the comparator arm.
- 6.39 The ipilimumab population in Trial MDX010-020 is not representative of the ipilimumab population who have progressed after being treated with first-line NIVO+IPI or nivolumab monotherapy. The PSCR agreed that there is limited to no data available specific to a comparison of the NIVO+IPI regimen vs sequencing of NIVO followed by IPI.
- 6.40 The ESC advised that the impact of observed second-line active treatments on OS in both arms over a 2-year model time horizon had been already captured by CA209-067. Figure 4 below shows that the model estimated a smaller OS advantage than the trial (the cost-effectiveness results are driven by the cost difference not the QALY difference). The model bore little relation to the observed trial data with respect to absolute or relative OS gains, as illustrated by the following figure.

Figure 4: Modelled overall survival compared with overall survival from Trial CA209-067



Source: compiled during the evaluation

6.41 The structure of the economic model was broadly similar to that in the previous submission, with the exception of the addition of a health state to capture progressions in the second-line setting and an adjustment of the time horizon from 10.12 years to 24 months. The resubmission has not addressed concerns raised by the PBAC previously (paragraphs 7.6 and 6.5.1, 5.10 nivolumab + ipilimumab PSD, November 2015 PBAC meeting), including:

- the unnecessarily complex approach to modelling the transitions between health states (for example, splitting of overall survival into pre-progression overall survival and post-progression overall survival); and
- the high absolute utility values for pre- and post-progression disease states.

6.42 A summary of the model structure and rationale is provided in Table 8 below.

Table 8: Summary of model structure and rationale

Time horizon	24 months in the model versus minimum 28 months follow up in the trial.
Outcomes	QALY, LYG
Methods used to generate results	Cohort expected value analysis, based on the PFS and OS estimates from CA209-067 and MDX010-020.
Health states	P0: 'Alive, pre progression'; P1: 'Alive post 1st progression'; P2: 'Alive post 2nd progression'; and dead. The model allowed for a splitting of overall survival into pre-progression overall survival and post-progression overall survival.
Cycle length	2 weeks
Transition probabilities	The following transition probabilities were based on CA209-067 <ul style="list-style-type: none"> • P0 to death based on OS data • P0 to P1 based on PFS data, less patients who have died (using OS data); The following transition probabilities were based on MDX010-020: <ul style="list-style-type: none"> • P1 and P2 to death based on OS data • P1 to P2 based on PFS data, less patients who have died (using OS data).
Discount rate	5% p.a. for costs and outcomes
Software package	Excel 2010

QALY = quality-adjusted life year gained; LYG = life year gained; PFS = progression-free survival; OS = overall survival.
Source: compiled during the evaluation

6.43 The key drivers of the model are provided in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Costing error	Incorrect cost entered for ipilimumab in the combination therapy arm	High, favours NIVO+IPI
Utilities	High values for model health states, and no disutility for AEs	High, favours NIVO+IPI
Second-line therapies	No active treatment in the nivolumab plus ipilimumab arm, and all patients receive treatment with ipilimumab after progression with nivolumab monotherapy in the comparator arm.	High, favours NIVO+IPI
Model structure	Splitting overall survival into pre-progression overall survival and post-progression survival	Linked to representation of second-line therapies

AE = adverse events; IPI = ipilimumab; NIVO = nivolumab.
Source: compiled during the evaluation

6.44 A major error was identified in the resubmission's model, where the total regimen cost of ipilimumab (12 weeks/4 cycles) was applied every cycle (3 weeks) in the comparator arm. This meant that the regimen cost for patients progressing in the comparator arm was four times what it should have been. The cost of ipilimumab was correctly applied in the NIVO+IPI arm. Correcting this error resulted in an incremental cost per patient of \$██████, rather than a cost saving of \$██████ as presented in the resubmission. All else being equal, this resulted in an ICER of more than \$200,000/QALY.

Table 10: Results of the economic evaluation

Component	NIVO+IPI followed by BSC	NIVO followed by IPI	Increment
Total costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
Revised ¹	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total QALYs	1.112	1.102	0.009
Total LYG	1.343	1.340	0.003
Incremental cost/extra QALY gained			Dominant
Revised incremental cost/extra QALY gained ¹			\$ [REDACTED]
Incremental cost/extra life-year gained			Dominant
Revised incremental cost/extra life year gained ¹			\$ [REDACTED]

BSC = best supportive care; IPI = ipilimumab; NIVO = nivolumab; QALY = quality-adjusted life year gained.

¹ Revised to correct for the resubmission's calculation error that applied the total regimen cost of ipilimumab (four three-weekly cycles) every cycle, resulting in the cost of ipilimumab being four-times higher than it should.

Source: Table 63 and Table 64, p156, Section D of the resubmission.

- 6.45 The PSCR acknowledged this error, and made two further modifications: i) inclusion of ipilimumab re-induction in the sequence arm (8.8% in MDX010-020) and ii) correction of the mean doses of ipilimumab for the NIVO+IPI arm (3.2 instead of 4). The resulting ICER was more than \$200,000/QALY gained. The ESC could not confirm this, as the changes to the model to achieve the second of these modifications would be complex, and so could not be independently verified without an electronic version of the modified model. However, the ESC noted that the revised ICER had not substantially reduced. The PSCR further noted that the small incremental difference in effect between the two treatment arms result in “an extremely sensitive economic model”, and stated that “reduction in the proposed cost of the NIVO+IPI regimen of 20% would equate to NIVO+IPI being dominant”.
- 6.46 The ESC advised that the adjustment of mean dose was reasonable. However, the inclusion of re-induction in the sequence arm, but not the combination arm, was not reasonable. As noted previously, the pre-PBAC response stated that the pivotal trial CA209-067 did not allow NIVO+IPI patients to be retreated with IPI and the sponsor maintained that retreatment with IPI should not be permitted under the PBS listing. The PBAC considered that, if the listing were to be implemented as requested, the re-induction treatment restriction for ipilimumab would need to be revised to ensure this intention is clear to prescribers.
- 6.47 As in the previous NIVO+IPI submission, base case utility values across all model states (progression-free, post-progression1 and post-progression 2) were 0.828 and 0.813 – 0.827 for the NIVO+IPI arm and the NIVO monotherapy arms, respectively. As noted previously, such absolute values are similar to values observed in the general population and the relative values between the arms do not align with the serious AE profiles as illustrated in Table 6 above. The PSCR argued that the study results show that there was no deterioration in health-related quality of life (HRQoL) even in the subgroup of patients experiencing grade 3/4 adverse events. The ESC considered that this may reflect the choice of HRQoL measure and the frequency and timing of the collection of HRQoL data, and it certainly did not support an improvement in utility values.
- 6.48 Correcting the current model for the likely utility effects of AEs would almost certainly result in NIVO+IPI followed by BSC being dominated by nivolumab monotherapy followed by ipilimumab monotherapy.

- 6.49 The ESC advised that a potentially valid approach would be to extrapolate PFS and OS using the CA209-067 study data, including perhaps an external estimate of second-line PFS. The ESC considered that it was likely that such an approach would not demonstrate cost-effectiveness (or even improved effectiveness) over the observed 2-year time horizon. This would need to be resolved before considering what time horizon would be appropriate, and whether the extrapolation over that time horizon would be valid.

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

- 6.50 The cost/patient/course of NIVO+IPI was estimated to be \$ [REDACTED]. This was compared with \$ [REDACTED] for the sequential treatment with nivolumab monotherapy followed by ipilimumab monotherapy upon progression. However, it should be noted that the estimation was based on the assumption that no patients receive active second-line treatment following progression on NIVO+IPI, while all surviving patients receive active second-line treatment with ipilimumab following progression on nivolumab monotherapy in the comparator arm. This is not reasonable. The PSCR acknowledged that approximately 30-35% of patients receiving NIVO monotherapy may not be well enough to receive IPI therapy in the second-line setting. The ESC considered that, as a result, the financial estimates also inappropriately reflected an unrealistic scenario that, in the absence of NIVO+IPI, all patients would receive the sequence of NIVO followed by IPI.
- 6.51 A summary of the estimated drug cost/patient/course for NIVO+IPI combination therapy, and for the nominated comparator, sequential therapy with nivolumab monotherapy followed by ipilimumab monotherapy, is presented in the table below.

Table 11: Summary of drug costs/patient/course for NIVO+IPI combination therapy

	Dosage/ average dose	Number of vials	Dispensed price per infusion	Mean no. infusions ^d	Total cost
NIVO+IPI combination therapy					
Nivolumab					
Induction phase	1 mg/kg Q3W Ave dose: 83.3 mg ^a	1 x 100 mg vial	Public: \$ ██████ ^b Private: \$ ██████ ^b Weighted: \$ ██████ ^b	3.25 ^d	\$ ██████
Continuing phase	3 mg/kg Q2W Ave dose: 250 mg ^a	1 x 100 mg vial 4 x 40 mg vials	Public: \$ ██████ ^b Private: \$ ██████ Weighted: \$ ██████	17.75 ^d	\$ ██████
Ipilimumab					
Induction phase	3 mg/kg Q3W Ave dose: 250 mg ^a	1 x 200 mg vial 1 x 50 mg vial	Public: \$ ██████ ^c Private: \$ ██████ ^c Weighted: \$ ██████ ^{b,c}	3.25 ^d	\$ ██████
Total cost/patient/course					\$ ██████
Sequential therapy with nivolumab and ipilimumab					
Nivolumab monotherapy	3 mg/kg Q2W Ave dose: 250 mg ^a	1 x 100 mg vial 4 x 40 mg vials	Public: \$ ██████ ^b Private: \$ ██████ ^b Weighted: \$ ██████ ^b	27.6 ^e	\$ ██████
Ipilimumab monotherapy	3 mg/kg Q3W Ave dose: 250 mg ^a	1 x 200 mg vial 1 x 50 mg vial	Public: \$ ██████ ^c Private: \$ ██████ ^c Weighted: \$ ██████ ^{b,c}	3.4 ^f	\$ ██████
Total cost/patient/course					\$ ██████

Q2W = every 2 weeks; Q3W = every 3 weeks

^a Based on a mean body weight of 83.3 kg

^b Based on the ex-manufacturer price for nivolumab IV infusion 40 mg in 4 mL = \$ ██████ and 100 mg in 10 mL = \$ ██████

^c Based on the effective ex-manufacturer price for ipilimumab as supplied by the Department of Health: injection concentrate for IV infusion 50 mg in 10 mL = \$ ██████ and ipilimumab injection concentrate for I.V. infusion 200 mg in 40 mL = \$ ██████

^d Derived using the mean number of doses received in CA209-067 and advice from seven oncologists on the sponsor's Advisory Board.

^e Based on the mean number of doses in the nivolumab monotherapy arm of CA209-067

^f Based on the mean number of doses in the ipilimumab monotherapy arm of MDX010-020

Source: Compiled during the evaluation

Estimated PBS usage & financial implications

- 6.52 This resubmission was not considered by DUSC. The resubmission presented a new financial analysis reflecting the change in the nominated comparator. The resubmission used a different approach to estimate the eligible population from that used in the previous submission. The proposed treatment algorithms and the assumed uptake of alternative treatment options also differed between the submissions.
- 6.53 The resubmission used an epidemiological approach to estimate the eligible population, based on DUSC utilisation data for ipilimumab and dabrafenib for unresectable Stage III and Stage IV malignant melanoma. The proportion of patients assumed to receive each treatment option, at each line of therapy, was based on expert opinion.
- 6.54 There was considerable uncertainty in the proportions of patients assumed to receive each treatment option, given that they were based on advice from seven expert members of the sponsor's Advisory Board. Limited detail was provided on the level of

agreement among the advisors and the rationale for the nominated proportions. These inputs were critical determinants of both the number of patients likely to be treated with NIVO+IPI and the cost-offsets resulting from substitution for sequential therapy with a PD-1 inhibitor and ipilimumab. The resubmission did not provide any sensitivity analysis around these estimates.

- 6.55 The resubmission used incidence data to estimate the number of patients likely to be treated each year. In doing so, rather than carrying over surviving patients to the following year, the resubmission assumed that all patients would complete all systemic anti-cancer therapy (up to three lines) within 12 months. Thus the full cost of each line of therapy received in both the first and any subsequent years was included in the estimates by being assigned to the incident year.
- 6.56 The cost per infusion for each treatment phase of NIVO+IPI combination therapy, first-line nivolumab monotherapy and second-line ipilimumab monotherapy were derived using the methodology outlined in Table 11, above. The resubmission did not use the most efficient vial combinations in both the induction and continuing phases of NIVO+IPI combination therapy, and for nivolumab monotherapy.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Number treated - Nov 2015 ^a					
Estimated net cost to government health budgets					
Net cost to PBS/RPBS Corrected during the evaluation ^{b,c}	\$	\$	\$	\$	\$
Net cost to PBS/RPBS Nov 2015* Previous commentary estimates ^d Previous PSCR estimates ^e	\$	\$	\$	\$	\$
Net cost to MBS Corrected during the evaluation ^f	\$	\$	\$	\$	\$
Net cost to MBS Nov 2015	\$	\$	\$	\$	\$
Cost to government of AE treatment	\$	\$	\$	\$	\$
Cost to government of AE treatment Nov 2015	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost to health budget Corrected during the evaluation ^{b,c,e}	\$	\$	\$	\$	\$
Net cost to health budget Nov 2015* Previous commentary estimates ^d Previous PSCR estimates ^e	\$	\$	\$	\$	\$

AE = adverse event; PSCR = Pre-subcommittee response

^a The previous submission used a different method to estimate the eligible population from the resubmission. There were also differences in the proposed treatment algorithms and the uptake of alternative treatment options between the submissions.

^b Patient numbers based on patients with BRAF V600 MT tumours, rather than patients with all BRAF MT tumours, as in the resubmission.

^c Costs revised using the effective ex-manufacturer price for ipilimumab, as supplied by the Department of Health, and using the revised dispensed prices per infusion, as set out in Table E.2.3 and Table E.3.3 of the Commentary.

^d Source: Table E.5.3, 5.10.COM.101

^e Source: Table 16, Paragraph 6.68 PSD November 2015 PBAC meeting.

^f Based on the number of infusions, rather than the number of scripts used in the resubmission.

* Note: The November 2015 submission originally nominated ipilimumab as the main comparator. This was revised to pembrolizumab in the PSCR.

Source: Compiled during the evaluation

- 6.57 Over five years, the estimated number of patients treated would be less than 10,000 and the net financial cost to the PBS would be more than \$100 million.
- 6.58 The financial estimates did not take into account patients who may require grandfathered treatment.

Financial Management – Risk Sharing Arrangements

- 6.59 The resubmission stated that the sponsor believes the current PD-1 inhibitor cap does not result in matching to the cost-minimisation conclusion of the PBAC about per patient cost being similar between ipilimumab and PD-1 inhibitors when patient

numbers proposed by the sponsors are used. The sponsor proposed that the Department and sponsors utilise the increased level of information now available (i.e. epidemiology publications, DUSC reports, PBS data) to revise and / or consolidate existing caps, which may in turn have an impact on the proposed methodology for addressing uncertainty in expenditure due to use of the combination of NIVO+IPI.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend listing concurrent use of nivolumab and ipilimumab (NIVO+IPI) for the treatment of unresectable Stage III or Stage IV malignant melanoma. In reaching this conclusion, the PBAC reiterated its previous view that the use of NIVO+IPI was associated with a modest improvement in PFS, but also a substantial increase in adverse events, and the data had not adequately demonstrated any advantage in terms of either quality of life or overall survival associated with combination immunotherapy. Furthermore, the PBAC considered that the resubmission's model presented an unacceptably high and uncertain ICER, and thus failed to demonstrate acceptable cost-effectiveness.
- 7.2 In terms of the clinical place in therapy, the PBAC noted that the resubmission considered that NIVO+IPI would be used in the first-line setting for patients with BRAF wild type melanoma, while the majority of patients with BRAF mutant melanoma would receive first-line combination BRAF/MEK inhibitor (or in some cases BRAF monotherapy) followed by second-line NIVO+IPI upon progression. However, the PBAC noted that the requested restriction included all patients with Stage III or IV unresectable metastatic melanoma, irrespective of BRAF status or treatment line. The PBAC noted the ESC's advice that there were no clinical data presented to support the use of NIVO+IPI in the second-line setting following a BRAF + MEK inhibitor, nor was this strategy included in the economic model presented in the resubmission, and that any PBS listing should therefore be restricted to patients with BRAF wild type melanoma only. However, the PBAC agreed with the PSCR (p2) that eligibility for NIVO+IPI in patients with BRAF mutant melanoma should generally be restricted to those who have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor), consistent with the current melanoma PBS listings for nivolumab and for pembrolizumab.
- 7.3 In reaching this view, the PBAC noted the findings of a recent network meta-analysis on immune checkpoint inhibitors and targeted therapies for metastatic melanoma (Pasquali et al, 2017) which showed that, where indicated for patients with melanoma, a combination of BRAF+MEK inhibitors was both more efficacious and less toxic than combination immunotherapy. The PBAC advised that patients with BRAF mutant melanoma should therefore receive first-line BRAF+MEK inhibitor treatment via the PBS. In addition, the PBAC noted the clinical expert input describing how these patients are likely to progress rapidly once stopping BRAF+MEK inhibitor treatment due to progression, and are therefore in particular need of the higher response rate of NIVO+IPI. Furthermore, the PBAC noted that the key trial of NIVO+IPI in melanoma (CA209-067) did not restrict eligibility by BRAF mutation status. Therefore, the PBAC also advised that second-line treatment with combination immunotherapy following disease progression with BRAF+MEK inhibitor

treatment would be appropriate for patients with BRAF mutant melanoma, where in line with clinical guidelines. Regardless, the PBAC agreed that this place in therapy would need to be reflected in a scenario analysis of the base case of the economic model to provide an informed basis to include this option in any PBS listing for NIVO+IPI.

- 7.4 The PBAC recalled it previously considered that the revised main comparator in the November 2015 submission, pembrolizumab monotherapy, was appropriate, but that the sequential use of a PD-1 inhibitor followed by ipilimumab, and dabrafenib ± trametinib for BRAF mutant patients, were also appropriate comparators (paragraph 7.3, 5.10 nivolumab plus ipilimumab Public Summary Document (PSD), November 2015 PBAC meeting). The PBAC noted that nivolumab, as monotherapy, was not PBS-listed for melanoma at the time of the previous submission. Whilst the PBAC considered that the main comparator in the resubmission (a treatment sequence of PD-1 inhibitor monotherapy followed by ipilimumab monotherapy upon disease progression) was still appropriate along the lines the committee had suggested previously, the PBAC noted that there was no direct randomised trial evidence presented to support this comparison. The PBAC noted that the pre-PBAC response (p1) stated that the sponsor used “the best available data to construct a naïve comparison”. The PBAC considered that the CA209-067 trial provided the best available data for the comparative effectiveness and safety of NIVO+IPI relative to nivolumab monotherapy in the first-line setting, with a variety of subsequent therapies used in both treatment arms, whilst the MDX010-020 trial for ipilimumab is not representative of the identified population who have progressed after being treated with first-line NIVO+IPI or nivolumab monotherapy because this trial recruited participants who had not received prior therapy. For these reasons, the PBAC considered that the best available evidence for an appropriate comparison including subsequent treatment following disease progression with each of these first-line alternatives remained CA209-067, because this trial would also provide relevant information on what second-line treatment options would likely be used after each of these first-line alternatives. This approach would also avoid the unrealistic assumptions for this comparison that 100% of patients who progress following initial PD-1 inhibitor monotherapy would receive ipilimumab, and that 100% of patients who progress following initial NIVO+IPI combination therapy would receive BSC. However, if there is evidence of some subsequent use of ipilimumab following NIVO+IPI in CA209-067, and this option is to be specifically excluded in the context of any PBS listing of NIVO+IPI, then an adjustment for this in the clinical and economic evaluations may also need to be considered. In addition, the re-induction treatment restriction for ipilimumab would need to be revised to ensure this intention is clear to prescribers.
- 7.5 The PBAC noted the updated clinical data provided from the September 2016 database lock of CA209-067. This data reaffirmed the PBAC’s previous conclusion that NIVO+IPI demonstrated an improvement in PFS over nivolumab monotherapy. Nonetheless, the OS data was still immature and showed no statistically significant effect for NIVO+IPI beyond that of nivolumab monotherapy, and there was no evidence of improved quality of life. The PBAC noted that future data cuts (3-year OS) are projected to be presented in September 2017. In the absence of evidence of an improvement in OS, and given the present PBS availability of nivolumab monotherapy, the PBAC considered that it was not unreasonable to wait for these further data to inform its consideration of the requested listing.

- 7.6 The PBAC noted that the resubmission did not present any updated safety data from CA209-067, but claimed that although the frequency and severity of AEs with the NIVO+IPI combination were higher than with either nivolumab or ipilimumab monotherapy, they were similar when considering the context of the sequence of nivolumab monotherapy followed by ipilimumab monotherapy. The PBAC considered that the evidence from CA209-067 was consistent with the general expectation that adding one medicine to another medicine to create a therapeutic combination would generally increase toxicity; this expectation was not unique to the combination in the requested listing. However, the important consideration was whether the increased toxicity was balanced by improved clinical benefits. In this regard, the PBAC noted the ESC's advice that NIVO+IPI combination patients who discontinued treatment due to AEs still derived a significant efficacy benefit (Schadendorf 2016). The PBAC also noted the consumer comments indicating patient acceptability of combination therapy toxicity and the substantial clinician engagement required to manage AEs. Overall, the PBAC concluded that, in the absence of a demonstrated improvement in OS or quality of life, the extent to which the inferior safety of NIVO+IPI was exceeded by improved clinical benefits remained unclear. In this context, the PBAC was also mindful of the TGA's decision and rationale for limiting marketing approval to patients with M1c melanoma or metastatic melanoma with elevated LDH levels, and proposed to reflect this more limited population in any PBS restriction.
- 7.7 The PBAC raised a number of concerns regarding the model structure and its inputs, and considered that the resulting revised ICER of more than \$200,000/QALY from the sponsor was unacceptably high and uncertain. The main concerns were:
- It was inappropriate to assume that the estimated extent of costs and effects of ipilimumab from the MDX010-020 trial would apply in patients whose melanoma had progressed following nivolumab monotherapy, because this trial recruited participants who had not received nivolumab.
 - A better source of trial data for the model would be CA209-067 including follow-up of participants for subsequent treatment options and costs beyond disease progression as well as health outcomes.
 - The modelled absolute or relative OS gains bore little relation to the non-significant OS gains observed from the CA209-067 trial data, appearing to potentially underestimate the possible overall survival benefit.
 - The unreasonable assumption that all nivolumab monotherapy patients would also receive post-progression ipilimumab inappropriately increased the costs of this arm in the model.
 - The unreasonable assumption that no NIVO+IPI patients received any post-progression therapies inappropriately decreased the costs of this arm in the model.
 - However, the combined effect of these two unreasonable assumptions was still not sufficient to increase the costs of the modelled comparator arm beyond those of the modelled NIVO+IPI arm.
 - The utility values were not reasonable, particularly in the NIVO+IPI arm where the excess toxicity of the combination therapy was not compatible with the lack of disutility in the model. Whilst the PSCR argued that the trial results did not show a decline in QoL among patients experiencing grade 3/4 AEs, the PBAC agreed with the ESC that this may reflect the choice of HRQoL measure and the frequency and timing of the collection of HRQoL data, and

the CA209-067 trial results certainly did not support an improvement in utility values.

- The model did not include the consequences of prior BRAF+MEK inhibitor therapy for patients with BRAF mutant melanoma in either arm. The implicit assumptions behind this exclusion would be either that such prior therapy would have no effect on subsequent therapy, or that such prior therapy would have an equal effect across both arms of the model. The evidence or rationale behind the assumption adopted would need to be provided for any further reconsideration by the Committee, together with a scenario analysis examining the sensitivity of the model to variations from this simplifying assumption.
- The clinical data supported a conclusion of improved PFS using NIVO+IPI therapy, but the two year time horizon excluded any consideration of long-term differences in PFS and possibly in OS. The PBAC noted that it had accepted a five year time horizon in the context of recommending PBS listing of pembrolizumab for melanoma (March 2015 PBAC meeting) and had advised that a ten year time horizon was not supported by the clinical evidence and favoured nivolumab significantly in both its rejection of PBS listing of nivolumab for melanoma (July 2015 PBAC meeting) and also in its previous rejection of the combination of nivolumab and ipilimumab for melanoma (November 2015 PBAC meeting).

Overall, these issues left the PBAC with considerable uncertainty as to the estimation of cost-effectiveness of NIVO+IPI therapy.

- 7.8 The PBAC considered that the financial estimates were uncertain, but considered that the financial impact was high (more than \$100 million over five years) for approximately 800 patients per year, which was particularly concerning in the context of an unacceptably high and uncertain estimate of cost-effectiveness.
- 7.9 The PBAC considered that any future resubmission should be a major submission to allow for evaluation of updated overall survival data and economic modelling.
- 7.10 The PBAC noted that although nivolumab is now TGA-approved for use in combination with ipilimumab, the ipilimumab approval has not been updated, so ipilimumab is still only approved as monotherapy for the treatment of patients with unresectable or metastatic melanoma. The PBAC suggested that the sponsor seek to update the TGA approval for ipilimumab in order to minimise the legal policy difficulties that would arise in the event that a PBS listing for ipilimumab in combination with nivolumab were to be implemented.
- 7.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final

PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor appreciates the consideration given to the current application and looks forward to the opportunity to submit further data to support the availability of nivolumab+ipilimumab as an option for melanoma patients.