7.05 NIVOLUMAB,
Injection concentrate for I.V. infusion 40 mg in 4 mL,
Injection concentrate for I.V. infusion 100 mg in 10 mL,
Opdivo®, Bristol-Myers Squibb,
PLUS
IPILIMUMAB,
Injection concentrate for I.V. infusion 50 mg in10 mL,
Injection concentrate for I.V. infusion 200 mg in 40 mL,
Yervoy®, Bristol-Myers Squibb

1 Purpose of Application

1.1 The resubmission requested a Section 100 (Efficient Funding of Chemotherapy) listing for nivolumab in combination with ipilimumab (NIVO+IPI) for the treatment of unresectable Stage III or Stage IV malignant melanoma, unrestricted by treatment line in patients with BRAF V600 mutation negative melanoma, and subsequent to BRAF±MEK inhibitor therapy in patients with BRAF V600 mutation positive melanoma. This differed from the previous two submissions considered by the PBAC in November 2015 and March 2017, which requested PBS listing for all patients with unresectable Stage III or Stage IV melanoma, irrespective of BRAF V600 mutation status or treatment line.

1.2 The requested listing was based on a cost analysis of NIVO+IPI compared with nivolumab monotherapy. The key components of the clinical issues addressed by the resubmission are presented in the table below.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients with unresectable Stage III or Stage IV malignant melanoma. In patients with BRAF mutant melanoma, eligibility would be restricted to patients whose melanoma has progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor).
Intervention	Initial combination phase: Nivolumab 1 mg/kg combined with ipilimumab 3mg/kg administered as an intravenous infusion every 3 weeks for up to 4 doses. Single agent maintenance phase: Nivolumab 3 mg/kg administered as an intravenous infusion every 2 weeks as long as clinical benefit is observed.
Comparator	PD-1 inhibitor monotherapy. Nivolumab was the comparator in the key trial presented in the resubmission (CA209067). The nominated comparator in the previous resubmission was PD-1 inhibitor monotherapy followed by ipilimumab monotherapy upon disease progression.
Outcomes	ORR, DOR, PFS, OS, AEs and QoL
Clinical claim	In patients with unresectable Stage III or Stage IV melanoma: NIVO+IPI is superior in terms of clinical efficacy (PFS and ORR) to nivolumab monotherapy, with an increasing positive trend in OS advantage over time, and NIVO+IPI is inferior in terms of safety compared with nivolumab monotherapy within the induction period, with manageable adverse events. No evidence was presented in the resubmission for patients with BRAF mutant melanoma who have progressed following BRAF inhibitor therapy.

AE = adverse event; DOR = duration of response; IPI = ipilimumab; NIVO = nivolumab; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death-1; PFS = progression free survival; QoL = quality of life.
Source: Table 2, p23-4 of the resubmission.

2 Requested listing

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Induction (combination) phase				
NIVOLUMAB 100 mg/10 mL injection, 1 x 10 mL vial 40 mg/4 mL injection, 1 x 4 mL vial	120 mg	3	Published price *$2,595.93* (public) *$2,669.46* (private) Effective price $[redacted] (public) $[redacted] (private)	Opdivo® Bristol-Myers 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	Published price *$47,479.99* (public) *$48,181.90* (private) Effective price $[redacted] (public) $[redacted] (private)	Yervoy® Bristol-Myers Squibb Australia Pty Ltd (BQ)
Continuing (single agent nivolumab) phase				
NIVOLUMAB 40 mg/4 mL injection, 1 x 4 mL vial 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	11	Published price *$7,580.13* (public) *$7,723.44* (private) Effective price $[redacted] (public) $[redacted] (private)	Opdivo® Bristol-Myers Squibb Australia Pty Ltd (BQ)

Dispensed prices calculated using PBS application fees as of 1 January 2018 (distribution fee $26.28, diluent free $5.21, preparation fee $103.83 and ready prepared dispensing fee $7.15). The resubmission applied a preparation fee of $83.83.
Source: Table 14, p45 of the resubmission; Excel workbook 'Appendix 2_BIM_NIVO+IPI.xlsx

Induction (combination) phase

Requested restriction for patients with BRAF V600 mutation negative melanoma	
Category/Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
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) treatment
Restriction:	☒Streamlined
Clinical criteria:	Patient must be receiving PBS-subsidised nivolumab and ipilimumab concomitantly for this condition, AND Patients must not have received prior treatment with ipilimumab or a PD-1 inhibitor *for this condition*, AND *Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1,* AND *Patients must not have ocular or uveal melanoma,* 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 *under this restriction*, AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks *under this restriction.*
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.

Requested restriction for patients with BRAF V600 mutation positive melanoma	
Category/Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
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) treatment
Restriction:	☒Streamlined

Clinical criteria:	*The condition must be positive for a BRAF mutation,* *AND* *The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor),* *OR* *Patient must be contraindicated to treatment with a BRAF inhibitor,* *OR* *Patient must have developed intolerance to a BRAF inhibitor of a severity necessitating permanent treatment withdrawal,* ~~Patient with BRAF V600 mutation positive melanoma must have progressed post BRAF ± MEK inhibitor treatment or are contraindicated/intolerant to BRAF ± MEK inhibitor treatment~~, AND Patient must be receiving PBS-subsidised nivolumab and ipilimumab concomitantly for this condition, AND Patients must not have received prior treatment with ipilimumab or a PD-1 inhibitor *for this condition,* AND *Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1,* AND *Patients must not have ocular or uveal melanoma,* 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 *under this restriction*, AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks *under this restriction*.
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.

Continuing (nivolumab single agent) phase

Category/Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Continuing (single-agent nivolumab) treatment
Restriction:	☒Streamlined
Clinical criteria:	*Patient must have previously received PBS-subsidised induction treatment with nivolumab and ipilimumab combination therapy for this condition,* ~~Patient must have previously been issued with authority prescriptions for induction phase ipilimumab and nivolumab combination therapy for this condition,~~ AND This drug must be the sole PBS-subsidised treatment for this condition, AND *Patient must not have developed disease progression whilst being treated with nivolumab and ipilimumab combination therapy for this condition,* ~~Patients 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.

2.1 The resubmission proposed a special pricing arrangement, with the effective ex-manufacturer prices for nivolumab and ipilimumab, when dispensed as components of combination therapy (both the induction and continuing phases), derived in the cost analysis presented in the resubmission. The PBAC noted that, compared to the dispensed price for maximum quantity (DPMQ) proposed in the March 2017 submission, the effective dispensed price of nivolumab in the July 2018 resubmission was reduced by [redacted]% in the induction phase and [redacted]% in the continuing phase and the price of ipilimumab was reduced by [redacted]%.

2.2 The PBAC noted that the resubmission differed from the previous two submissions as it proposed separate restrictions for patients with BRAF V600 mutation negative and BRAF V600 mutation positive melanoma for the induction treatment phase, and specified that patients with BRAF mutant melanoma should have progressed following BRAF inhibitor therapy. In the previous submissions, the requested restriction did not differentiate eligibility criteria for patients with BRAF mutant melanoma from those with BRAF wild type melanoma.

2.3 The separate restriction for patients with BRAF mutant melanoma in the resubmission was consistent with the PBAC's view that the 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 (paragraphs 7.2 and 7.3, 7.06 nivolumab plus ipilimumab Public Summary Document (PSD), March 2017 PBAC Meeting). However, no comparative evidence was provided in the resubmission for NIVO+IPI versus nivolumab monotherapy in patients with BRAF mutant melanoma who have progressed following BRAF inhibitor therapy. The pre-Sub-Committee Response (PSCR) indicated that this restriction was requested to align with the PBAC's advice, but that the sponsor intends to explore the potential for NIVO+IPI to be PBS listed in the future for the first-line treatment of patients with BRAF mutant melanoma.

2.4 The resubmission also requested grandfathering provisions for eligible patients who commence NIVO+IPI therapy before the requested listing is implemented. It was estimated that up to 260 patients enrolled in the sponsor's patient access program may be eligible for NIVO+IPI under this provision. The ESC noted that no details were provided on how this estimate was derived. The pre-PBAC response provided further details, which suggested that that 315 patients were eligible for grandfathering at the time of PBAC consideration in July 2018, that 268 patients would be eligible in December 2019, and that up to 329 patients might be eligible in the intervening 18 months.

2.5 The requested PBS restriction was in line with the recently updated TGA-approved indication which included all patients with unresectable or metastatic melanoma, irrespective of M stage or lactic dehydrogenase (LDH) level.

2.6 Previously untreated patients with BRAF mutant type tumours were included in the key trial presented in the resubmission (CA209067). This was not consistent with the proposed PBS listing in the resubmission, which restricted eligibility for PBS-subsidised NIVO+IPI in patients with BRAF mutant type tumours to those who had progressed following first line BRAF inhibitor therapy.

2.7 The PBAC noted that no clinical evidence was provided for patients with an Eastern Cooperative Oncology Group (ECOG) performance status of >1, patients with ocular melanoma or for patients who had received prior systemic therapy for melanoma. Therefore, the PBAC recommended the listing restrict use to reflect these limitations in clinical evidence.

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

3 Background

Registration status

3.1 Both nivolumab and ipilimumab are currently registered, as monotherapy, for the treatment of patients with unresectable or metastatic melanoma.

3.2 Nivolumab, in combination with ipilimumab, was registered by the TGA and listed on 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).

3.3 An application was submitted to the TGA to broaden the above combination indication to include all patients with unresectable or metastatic melanoma, irrespective of M stage or LDH level. The TGA approved the registration of the combination for the following indication:

> Opdivo (nivolumab), in combination with Yervoy (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma.

3.4 Both the TGA application to broaden the indication and the current PBAC application were based on updated 3-year data from the CA209067 trial. The TGA application which resulted in registration of the subgroup of patients with metastatic (Stage IV) melanoma with M1c disease or elevated LDH was based on an interim analysis from the CA209067 trial.

Previous PBAC consideration

3.5 This was the third consideration of NIVO+IPI by the PBAC for the treatment of unresectable Stage III or Stage IV malignant melanoma. The previous two submissions were considered by the PBAC in November 2015 and March 2017.

3.6 Pembrolizumab and nivolumab, two programmed cell death 1 (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.

3.7 The table below briefly summarises the key outstanding matters from the most recent PBAC considerations (at the March 2017 PBAC meeting) and how the resubmission addressed those concerns.

Table 2: Summary of key outstanding matters of concern

Matter of concern (March 2017 PBAC PSD)	How the resubmission addresses it
[paragraph 7.2] The requested restriction included all patients with Stage III or IV unresectable metastatic melanoma, irrespective of BRAF status or treatment line. However, there were no clinical data presented to support the use of NIVO+IPI in the 2L setting following a BRAF + MEK inhibitor. [Paragraph 7.3] The PBAC noted the findings of a recent network meta-analysis (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. In addition, the PBAC noted the clinical need of NIVO+IPI in BRAF MT patients following failure of BRAF+MEK inhibitor treatment. The PBAC advised that 2L treatment with combination immunotherapy following disease progression with BRAF+MEK inhibitor treatment would be appropriate for patients with BRAF MT melanoma.	The resubmission revised the proposed restrictions to include: • 1L treatment of patients with BRAF WT melanoma, and • 2L treatment of patients with BRAF MT melanoma who have progressed following treatment with a BRAF inhibitor (± a MEK inhibitor) No data was presented to demonstrate the treatment effect of NIVO+IPI compared with nivolumab for treatment of BRAF MT melanoma in patients with disease progression on/after treatment with BRAF inhibitor ± MEK inhibitor.
[Paragraph 7.1] The use of NIVO+IPI was associated with a modest improvement in PFS, but also a substantial increase in AEs, and the data had not adequately demonstrated any advantage in terms of either QoL or OS associated with combination immunotherapy. [Paragraph 7.5] The PBAC noted the updated OS data presented in this submission was immature and showed no statistically significant effect for NIVO+IPI beyond that of NIVO monotherapy. [Paragraph 7.6] In the absence of a demonstrated improvement in OS or QoL, the extent to which the inferior safety of NIVO+IPI was exceeded by improved clinical benefits remained unclear. In this context, the PBAC was mindful of the TGA's decision and rationale for limiting marketing approval to patients with poor prognosis and proposed to reflect this more limited population in any PBS restriction.	The resubmission presented updated 3-year data from the key trial CA209067. The updated HR for OS was 0.85 (95% CI: 0.68, 1.07). The updated data from CA209067 were very similar to those presented in the previous resubmission. There was no statistically significant difference in OS with first-line NIVO+IPI compared with first-line nivolumab monotherapy. The resubmission did not provide any clinical evidence that NIVO+IPI confers any benefit over nivolumab monotherapy in terms of quality of life. The resubmission argued that while NIVO+IPI was inferior to nivolumab monotherapy in terms of safety within the induction period, the AEs are mostly short-term and are manageable. This does not alter the fact that more patients receiving NIVO+IPI combination therapy experience these AEs, that a considerable proportion require immune-modulating medication to treat these AEs, and more patients will have ongoing unresolved adverse events compared to patients receiving nivolumab monotherapy.
[Paragraph 7.8] The PBAC considered that the financial estimates were uncertain, but considered that the financial impact was high (more than $100 million over 5 years), which was particularly concerning in the context of an unacceptably high and uncertain estimate of cost-effectiveness.	The resubmission presented an updated financial analysis. The estimated cost to the government health budgets was around $60 - $100 million over the first 6 years of listing. The resubmission has requested a subsidisation cap for NIVO+IPI that is separate to the existing PD-1 inhibitor monotherapy subsidisation cap. If NIVO+IPI is not included under the subsidisation cap that currently applies to PD-1 inhibitor monotherapy for melanoma, the cost offsets resulting from substitution of NIVO+IPI for PD-1 inhibitor monotherapy, as applied in the resubmission, would not be realised. As a result, the net cost to the PBS/RPBS would be considerably higher than estimated in the resubmission.

1L = first-line; 2L = second-line; AE = adverse event; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; MT = mutant type; NIVO = nivolumab; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PD-1 = programmed cell death 1; PFS = progression-free survival; PSD = public summary document; QoL= quality of life; WT = wild type
Source: Revised based on Table 1, pp17-22 of the resubmission.

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

4 Population and disease

4.1 Australia and New Zealand have the highest rates of melanoma in the world. The target population was patients with unresectable Stage III or Stage IV melanoma.

4.2 Both nivolumab and ipilimumab monotherapy are currently listed on the PBS for unresectable Stage III or Stage IV melanoma. 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.

4.3 The resubmission proposed 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. The ESC noted that this was due to the proposed PBS restrictions, which stipulate treatment in first- versus later-line settings based on BRAF V600 mutation status.

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

5 Comparator

5.1 The resubmission nominated PD-1 inhibitor monotherapy (e.g. nivolumab and pembrolizumab) as the main comparator for NIVO+IPI, in the first line setting for patients with BRAF wild type melanoma and second line for patients with BRAF mutant type melanoma who have progressed (or are contraindicated/intolerant to) treatment with a BRAF inhibitor ± MEK inhibitor. The PBAC previously considered that nivolumab was non-inferior in terms of both comparative effectiveness and safety to pembrolizumab for treatment of unresectable Stage III or Stage IV malignant melanoma (Paragraph 7.5, 7.14 nivolumab PSD, November 2015 PBAC Meeting). The PBAC considered that the nominated comparator was appropriate.

5.2 Nivolumab was the comparator in the key trial presented in the current and previous resubmission (CA209067). No comparative evidence was provided in the resubmission 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.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The sponsor discussed how the combination of NIVO+IPI was used in practice, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative in terms of how adverse events and discontinuation from NIVO+IPI therapy were managed, including advice that if patients developed toxicity related to the ipilimumab component, both NIVO+IPI were usually ceased.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (310), health care professionals (12) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with NIVO+IPI including the rapid clinical benefits. The incidence and severity of adverse events was noted. The PBAC acknowledged the high consumer and clinical demand for the combination therapy.

6.3 The PBAC noted the correspondence received from Melanoma Patients Australia and the Melbourne Melanoma Project supporting access to NIVO+IPI in clinical practice. The PBAC specifically considered the advice from the Melbourne Melanoma Project that was supportive of NIVO+IPI as a first-line treatment for BRAF mutant patients and noted the toxicity issues with the combination therapy, but stated that clinicians were becoming well versed in dealing with them. The PBAC noted that the advice was supportive of the evidence provided in the submission.

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 could not present the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)[*] for NIVO+IPI as the data was immature and the median survival times in the trial, CA209067, had not yet been reached. In addition, the CA209067 trial was not powered to compare survival difference between NIVO+IPI and nivolumab monotherapy. The Medical Oncology Group of Australia Melanoma Sub-Committee also supported the NIVO+IPI submission, particularly for patients with brain metastases and mucosal melanoma. The Sub-Committee stated that debate surrounding the degree of benefit compared with the toxicity and financial cost of NIVO+IPI versus nivolumab monotherapy was ongoing, but that the combination was the most effective melanoma immunotherapy to date, with significant, but manageable, toxicity. The Sub-Committee also stated that NIVO+IPI had potential positive economic consequences, as patients with significant toxicity while remaining in response could discontinue treatment, and combination patients were less likely to require subsequent

[*] Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology. 2017:28:2340-2366.

therapies. The Sub-Committee also requested freedom to select targeted or immunotherapy as first-line treatment for BRAF-mutant metastatic melanoma, stating that there is no robust data to suggest targeted therapy should be used first line, and that meta-analyses based on indirect comparisons such as those by Pasquali 2017[†] are flawed as they are largely based on superseded targeted and immunotherapy drug regimens.

Clinical trials

6.5 The resubmission was based on one head-to-head, randomised, double blind, three-arm trial comparing NIVO+IPI combination therapy, nivolumab monotherapy and ipilimumab monotherapy in patients with previously untreated unresectable Stage III or Stage IV melanoma (CA209067).

6.6 This trial was presented in both the original submission considered by the PBAC in November 2015 (9 months minimum follow-up) and the previous resubmission in March 2017 (28 months minimum follow-up). The PBAC noted that the current resubmission presented data from the May 2017 database lock (36 months minimum follow-up).

6.7 The resubmission also presented a supplementary trial comparing NIVO+IPI combination therapy with nivolumab monotherapy in patients with melanoma brain metastases (Long 2018). Long 2018 was an open-label phase 2 trial conducted at four cancer centres in Australia. The trial included three cohorts of patients with active melanoma brain metastases (n=76):

- Cohort A (n=35): NIVO+IPI in asymptomatic previously untreated (no previous local brain-directed therapy) patients;
- Cohort B (n=25): Nivolumab monotherapy in asymptomatic previously untreated patients; and
- Cohort C (n=16): Nivolumab monotherapy patients with poor prognostic features.

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

[†] Pasquali S, Chiarion-Sileni v, Rossi CR, et al. Immune checkpoint inhibitors and targeted therapies for metastatic melanoma: A network meta-analysis. Cancer Treat Rev. 2017;54:34-42.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
CA209067	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. Interim Clinical Study Report: database lock February 2015 Topline Report: database lock September 2016 Clinical Study Report: database lock May 2017 Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma Wolchok JD, Chiarion-Sileni V, Gonzalez R et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma.	 19 June 2015 18 October 2016 - NEJM 2015; 373 (1): 23-34. NEJM 2017; 377 (14):1345-1356.
Supplementary studies		
Long 2018	Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study.	Lancet Oncology 2018. Article in Press

Source: Table p51 and Table 19, p56 of the resubmission

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

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
NIVO+IPI vs NIVO monotherapy					
CA209067	630*	R, DB Minimum duration of FU 36 months	Low	Untreated unresectable or metastatic melanoma	PFS, OS
Long 2018	76	OL Median duration of FU: Cohort A: 14 months Cohort B: 17 months Cohort C: 31 months	High	Patients with brain metastases who are asymptomatic previously untreated or with poor prognostic features	PFS rate and OS rate at 6 months

DB = double blind; FU = follow-up; IPI = ipilimumab; NIVO = nivolumab; OL = open label; OS = overall survival; PFS = progression free survival; R = randomised.

* This number of patients is only for NIVO+IPI arm and NIVO monotherapy arm (314 and 316 respectively). Patients treated with ipilimumab monotherapy were not considered in this table.

Source: compiled during the evaluation based on Sections 2.3 and 2.4 of the resubmission.

6.10 As CA209067 was a randomised, double-blind trial, with minimal loss to follow-up, the risk of bias was low. Given the deviations from the randomisation procedure, the low number of patients in each cohort and the open-label nature of Long 2018, the overall risk of bias in this study was high.

6.11 The primary objective of CA209067 was to evaluate the safety and effectiveness of nivolumab monotherapy and NIVO+IPI in comparison with ipilimumab monotherapy. The comparison between NIVO+IPI combination therapy and nivolumab monotherapy was included as a secondary endpoint. The PBAC noted that the trial was not designed for a formal statistical comparison between the NIVO+IPI and the nivolumab monotherapy treatment arms.

6.12 The PBAC noted that the use of BRAF inhibitors and PD-1 inhibitors post-progression in CA209067 did not reflect the current PBS listings for these drugs, which are precluded in patients who have received prior PBS-subsidised treatment with a PD-1 inhibitor.

6.13 The PBAC also noted that CA209067 excluded patients with an ECOG performance status >1, active brain metastases and ocular melanoma. Long 2018, which assessed patients with brain metastases, used a non-randomised cohort and was open-label.

Comparative effectiveness

6.14 The table below compares the overall survival (OS) results presented in the previous resubmission (September 2016 database lock; minimum follow-up 28 months) with the updated OS data from the May 2017 database lock (minimum follow-up 36 months).

Table 5: Overall survival results: CA209067 (ITT)

	CA209067 Minimum follow-up 28 months (March 2017 resubmission)		CA209067 Minimum follow-up 36 months (Current resubmission)	
	NIVO+IPI N = 314	Nivolumab N = 316	NIVO+IPI N = 314	Nivolumab N = 316
Number of events, n (%)	128 (40.8%)	142 (44.9%)	139 (44.3%)	158 (50.0%)
Median OS (months), (95% CI)	NA	NA (29.1, NA)	NA (38.18, NA)	37.59 (29.08, NA)
Hazard Ratio (95% CI)[a, b] Stratified Log-rank p-value	0.88 (0.67, 1.12) NR		0.85 (0.68, 1.07) 0.1908	
OS rate, % (95% CI)	NIVO+IPI N = 314		Nivolumab N = 316	
OS rate 6 months	86% (81, 89)		85% (81, 89)	
OS rate 9 months	80% (75, 84)		79% (74, 83)	
OS rate 12 months	73% (68, 78)		74% (69, 79)	
OS rate 18 months	68% (62, 73)		65% (60, 70)	
OS rate 24 months	64% (59, 69)		59% (53, 64)	
OS rate 36 months	58% (52, 63)		52% (46, 57)	

CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; ITT = intention to treat; NA = not assessable; NIVO = nivolumab; NR = not reported; OS = overall survival; PD-L1 = programmed death-ligand 1.

[a] NIVO+IPI versus nivolumab monotherapy

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

Source: Table 33, p 79 of the resubmission; Table 4, paragraph 6.15, 7.06 nivolumab and ipilimumab PSD, March 2017 PBAC Meeting.

6.15 At a minimum follow-up of 36 months, the hazard ratio (HR) for OS for NIVO+IPI versus nivolumab monotherapy in the intention to treat (ITT) population was 0.85 (95% confidence interval (CI): 0.68, 1.07; Log-rank p=0.1908). The resubmission noted that CA209067 was not powered to detect a difference in OS between NIVO+IPI and nivolumab monotherapy, and that the incremental difference in OS rate between the arms had widened over time, favouring NIVO+IPI over nivolumab monotherapy. The OS results were very similar to those presented in the March 2017 resubmission and were still relatively immature; therefore, the difference in median OS between the two treatment arms could not be determined.

6.16 The progression free survival (PFS) results across the three submissions are summarised below.

Table 6: Progression free survival: CA209067 (ITT)

	CA209067					
Minimum follow-up	9 months		28 months		36 months	
	NIVO+IPI N = 314	NIVO mono N = 316	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%)	179 (57.0%)	199 (63.0%)
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)	11.5 (8.7, 19.3)	6.9 (5.1, 9.7)
Hazard ratio (95% CI)[a]	**0.74 (0.60, 0.92)**		**0.76 (0.62, 0.94)**		**0.78 (0.64, 0.96)**	

CI = confidence interval; IPI = ipilimumab; ITT = intention to treat; mono = monotherapy; NIVO = nivolumab; PFS = progression free survival.

[a] NIVO+IPI versus nivolumab monotherapy.

Source: Table 34, p81 of the resubmission; Table 5, paragraph 6.18, 7.06 nivolumab and ipilimumab PSD, March 2017 PBAC Meeting.

6.17 At a minimum follow-up of 36 months, NIVO+IPI was associated with an improvement in median PFS of 4.6 months. The PBAC noted that the updated PFS results from the May 2017 database lock were similar to those presented in the March 2017 resubmission.

6.18 While the subgroup analyses in CA209067 were underpowered, there was no evidence that NIVO+IPI conferred any benefit over nivolumab monotherapy in patients with BRAF wild type melanoma, in terms of either OS (HR = 0.94; 95% CI: 0.72, 1.22) or PFS (HR = 0.89; 95% CI: 0.70, 1.14). In comparison, in patients with BRAF mutant type melanoma the HR for OS was 0.69 (95% CI: 0.44, 1.07) and for PFS was 0.59 (95% CI: 0.42, 0.85).

6.19 In CA209067, health-related quality of life (QoL) was assessed using European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-30) and the European Quality of Life-5 dimensions (EQ-5D). From the first assessment post-baseline (Week 5) to Week 19 the completion rates of both questionnaires in the NIVO+IPI arm were >13% lower than in the nivolumab monotherapy arm, with completion rates of 52.7% and 77.5% at week 13 in the NIVO+IPI and nivolumab monotherapy arms, respectively, for both the EORTC-QLQ-C30 and the EQ-5D. Completion rates were subsequently similar across the treatment arms. The baseline characteristics of those not contributing to the QoL data were not provided.

6.20 The PBAC noted that there was a slight decrement in QoL scores at Week 5 but scores stabilised towards Week 25 and that the low response rate in the NIVO+IPI arm compared to the nivolumab monotherapy arm over the first 19 weeks of the trial may be due to the high rate of Grade 3-4 and severe adverse events (AEs) associated with the combination phase of NIVO+IPI therapy. As patients experiencing these events were less likely to complete the assessments, there was considerable potential for attrition bias over this period.

6.21 The TGA clinical evaluator noted that the final CSR for CA209067 stated that, in the NIVO+IPI group, clinically meaningful deterioration (i.e. mean change in score from baseline ≥10 points) was observed in EORTC-QLQ-C30 role functioning (Weeks 7, 17, 91 and 115), fatigue (Weeks 7 and 103) and appetite loss (Week 7) (TGA Clinical

evaluation report, Attachment 9a to the resubmission). The TGA evaluator stated that, while only limited updated quality of life data were presented in the updated CSR, there appeared to be a sustained, longer term loss of quality of life with the combination, noting that a substantial decline in role functioning was still evident after 151 weeks in the NIVO+IPI arm (TGA Clinical evaluation report, Attachment 9a to the resubmission). These details were considered by the PBAC.

6.22 The effectiveness results from Long 2018 are summarised below.

Table 7: Summary of outcomes in Long 2018

	NIVO+IPI	Nivolumab monotherapy	
	Cohort A[a] N = 35	Cohort B[a] N = 25	Cohort C[b] N = 16
Intracranial response			
Objective response rate[c], n (%)	16 (46%)	5 (20%)	1 (6%)
Intracranial PFS			
Median PFS, months (95% CI)	NA (2.9, NA)	2.5 (1.7, 2.8)	2.3 (1.4, 4.3)
PFS rate 6 months (95% CI)[d]	53% (38%, 73%)	20% (9%, 44%)	13% (3%, 46%)
Extracranial PFS			
Median PFS, months (95% CI)	13.8 (4.9, NA)	2.6 (1.8, 13.8)	2.6 (2.1, 13.6)
PFS rate 6 months (95% CI)[d]	51% (35%, 76%)	35% (19%, 64%)	19% (5%, 65%)
Overall survival			
Median OS, months (95% CI)	NA (8.5, NA)	18.5 (6.9, NA)	5.1 (1.8, NA)
OS rate 6 months (95% CI)[d]	78% (65%, 94%)	68% (52%, 89%)	44% (25%, 76%)

CI = confidence interval; IPI = ipilimumab; NA = not assessable; NIVO = nivolumab; OS = overall survival; PFS = progression free survival

[a] Patients with asymptomatic untreated melanoma brain metastases

[b] Patients symptomatic or treated brain metastases or leptomeningeal disease. Not randomised.

[c] Proportion of patients with a confirmed best intracranial response of complete or partial response at or after week 12.

[d] Estimated from Kaplan-Meier curve

Source: Table 3, Attachment 10 to the resubmission; Table 2, p5 Long 2018.

6.23 Of patients with asymptomatic, untreated melanoma brain metastases, a greater proportion of patients receiving NIVO+IPI achieved a best intracranial response of complete or partial response (46%), compared with those receiving nivolumab monotherapy (20%). These results should be interpreted with caution, given the low number of patients in the trial and the relatively high risk of bias due to deviation from the randomisation procedure and the open-label nature of the trial.

Comparative harms

6.24 The table below summarises the updated data on the number of drug-related AEs leading to discontinuation of study treatment, deaths due to study drug toxicity, and drug-related AEs of interest in CA209067.

Table 8: Summary of safety outcomes in CA209067

	CA209067			
	Minimum follow-up 9 months[a]		Minimum follow-up 36 months	
	NIVO+IPI N = 313 n (%)	Nivolumab monotherapy N = 313 n (%)	NIVO+IPI N = 313 n (%)	Nivolumab monotherapy N = 313 n (%)
Overall drug-related AEs				
Any AE	299 (96%)	257 (82%)	300 (96%)	270 (86%)
Any serious AE	150 (48%)	25 (8%)	NR	NR
Any severe AE (Grade ≥3)	172 (55%)	51 (16%)	NR	NR
AE leading to discontinuation	114 (36%)	24 (8%)	123 (39%)	37 (12%)
Death due to study drug toxicity	0	1 (0.3%)	2 (0.6%)	1 (0.3%)
Drug-related AEs of special interest				
Endocrine	94 (30.0%)	45 (14.4%)	-	-
Gastrointestinal	145 (46.3%)	61 (19.5%)	-	-
Hepatic	95 (30.4%)	40 (12.8%)	-	-
Pulmonary	22 (7.0%)	7 (2.2%)	-	-
Renal	17 (5.4%)	10 (3.2%)	-	-
Skin	185 (59.1%)	167 (53.4%)	-	-

AE = adverse event; IPI = ipilimumab; NIVO = nivolumab; NR = not reported.

[a] Data from the February 2015 database lock

Source: Table 37, p 90 of the resubmission; p162 CSR Binder 2, Attachment 12b to the resubmission.

6.25 The updated safety data were consistent with those presented in the original submission (no new safety data were presented in the March 2017 resubmission).

6.26 In Long 2018, of patients with asymptomatic, untreated melanoma brain metastases, Grade 3 or 4 treatment related AEs occurred in 19/35 (54%) patients receiving NIVO+IPI (Cohort A) and 4/25 (16%) receiving nivolumab monotherapy (Cohort B); 2/16 (13%) of patients with melanoma brain metastases with poor prognostic features experienced Grade 3 or 4 AEs related to nivolumab monotherapy.

6.27 The PBAC again considered that combination treatment with NIVO+IPI has a significantly inferior safety profile compared to pembrolizumab monotherapy, nivolumab monotherapy or ipilimumab monotherapy. The PBAC noted that there were limited new safety data presented in the resubmission, and reiterated that there were significantly higher rates of serious AEs with NIVO+IPI combination therapy compared to nivolumab monotherapy at nine months, 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 PSD, November 2015 PBAC meeting).

6.28 The PBAC acknowledged that clinicians were becoming better versed in treating the adverse events, particularly in the urban setting, but noted that safety in the more rural and remote settings and private hospitals remained a concern. The PBAC noted that there was a need for improved access to high-cost rescue therapies in these

settings, for example infliximab for treatment-induced colitis which is not currently PBS-funded for this indication nor routinely available on hospital formularies.

Benefits/harms

6.29 A summary of the comparative benefits and harms for NIVO+IPI versus nivolumab monotherapy in treatment naïve patients is presented in the table below.

Table 9: Summary of comparative benefits and harms for NIVO+IPI and nivolumab monotherapy* – CA209067

Benefit – PFS					
	NIVO+IPI	**NIVO**	**Absolute difference**		**HR (95% CI)**
Progressed or died	179/314 (57.0%)	199/316 (63.0%)	-		0.78 (0.64, 0.96)
Median PFS (months)	11.5 (8.7, 19.3)	6.9 (5.1, 9.7)	4.6		-
Benefit – OS					
Death	139/314 (44.3%)	158/316 (50.0%)	-		0.85 (0.68, 1.07)
Median OS (months)	NA (38.18, NA)	37.59 (29.08, NA)	-		-
Harms					
	NIVO+IPI	**NIVO**	**RR (95% CI)**	**Event rate/100 patients**	**RD (95% CI)**
				NIVO+IPI / **NIVO**	
Study-drug related AEs					
AE leading to discontinuation	123/313 (39%)	37/313 (12%)	3.32 (2.38, 4.64)	39 / 12	0.27 (0.21, 0.34)

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 follow-up 36 months.
Source: Compiled during the evaluation based on Section 2.5 of the resubmission

6.30 On the basis of the direct evidence presented in the resubmission, there would be approximately 4.6 months increase in median progression-free survival in patients treated with NIVO+IPI in comparison with nivolumab monotherapy in the first-line setting, over a minimum 36 months follow-up. 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:

- approximately 27 additional patients would experience a treatment-related AE leading to discontinuation of treatment over a minimum duration of follow-up of 36 months.

Clinical claim

6.31 The PBAC noted that the resubmission presented a similar clinical claim to the previous submissions, describing NIVO+IPI as superior in terms of PFS and objective response rate (ORR) compared with nivolumab monotherapy, with an increasing positive trend in OS advantage over time, and inferior in terms of safety compared to nivolumab monotherapy within the induction period, with manageable adverse events. The PBAC considered that the updated data from CA209067 were very similar to those presented in the previous resubmission and did not alter the conclusions regarding the comparative effectiveness and safety of NIVO+IPI compared with nivolumab monotherapy.

6.32 The data presented in the resubmission did not adequately support a claim of superior comparative effectiveness in the proposed PBS population:

- The resubmission did not provide any evidence for the comparative effectiveness of second-line NIVO+IPI versus second-line nivolumab monotherapy in patients with BRAF mutant type melanoma who have progressed following BRAF±MEK inhibitor therapy;
- The updated data from CA209067 failed to demonstrate a statistically significant difference in OS with first-line NIVO+IPI compared with first-line nivolumab monotherapy (HR = 0.85; 95% CI: 0.68, 1.07), although the trial was not adequately powered for this comparison;
    - There was no evidence of any additional OS or PFS benefit with NIVO+IPI compared with nivolumab monotherapy in patients with BRAF wild type melanoma (OS HR = 0.94; 95% CI: 0.72, 1.22; PFS HR = 0.89; 95% CI 0.70, 1.14);
    - The PSCR reiterated that CA209067 was not statistically powered to make a formal comparison between NIVO+IPI and NIVO monotherapy in the total population or a BRAF subgroup. It presented a post-hoc assessment[‡] indicating that BRAF mutant patients across regions (n=102), as well as BRAF wildtype patients in the USA (n=26) demonstrated OS benefit consistent with the ITT population (n=313) for the NIVO+IPI arm relative to the NIVO arm. A similar OS benefit was not observed in the EU population in BRAF wildtype patients (n=123). It postulated that the EU BRAF wildtype patients had a higher baseline burden of disease (M1c, elevated LDH, and larger tumour size) and were more likely to have received only one dose of NIVO+IPI relative to the overall study population. Early deaths in the EU patients with BRAF wildtype tumours may be attributed to the combination of poor prognostic factors and insufficient time to benefit from therapy. The large relative contribution of the EU patients to the BRAF wildtype subgroup (123/212, 57%) may have skewed the overall results in the BRAF wildtype subgroup.
    - The ESC noted that the PSCR did not provide details on how the assessment was conducted and the results could not be validated. The ESC was concerned that these were post hoc subgroup analyses, and randomisation did not appear to be stratified by region. As the baseline demographic and disease characteristics of the patients in each subgroup were not provided, it was not possible to assess whether other factors may have been contributing to the potential difference in outcomes across regions. Furthermore, as the PSCR did not provide a comparison of the disease characteristics of the proposed Australian population with those in the EU and USA subgroups in the trial, it was not possible to assess whether Australian patients are likely to

[‡] The PSCR stated that this assessment was presented at ESMO 2017 (Grob poster 1222PD).

be more similar, on average, to the USA or the EU patients in the trial in terms of disease stage at initiation of treatment.

- There was no clinical evidence that NIVO+IPI confers any benefit over nivolumab monotherapy in terms of quality of life, while it was associated with clinically meaningful deterioration in some measures. The PSCR reiterated that the submission did not claim that NIVO+IPI conferred any benefit over nivolumab monotherapy in terms of quality of life. The ESC considered that in the absence of evidence of any improvement in QoL or OS, the clinical importance of a gain in median PFS of 4.6 months is unclear. The ESC advised that this was an important consideration given that the NIVO+IPI group did report clinically meaningful deterioration (role functioning, fatigue and appetite loss) over 7 – 115 weeks (refer to paragraph 6.16 above).

6.33 The pre-PBAC response and PSCR also reiterated that the resubmission, despite claiming that NIVO+IPI is superior in terms of efficacy compared to nivolumab monotherapy, did not claim any efficacy advantages in the economic evaluation.

6.34 As per its previous considerations, the PBAC reiterated that NIVO+IPI combination therapy demonstrated superior comparative effectiveness in terms of a gain in PFS. The PBAC considered the clinical significance of the gain in PFS to be uncertain in terms of improved QoL or predicting any effect on OS; however, noted that the trial was not powered for the OS comparison.

6.35 As per its previous considerations, the PBAC considered that the claim of inferior comparative safety was reasonable, noting that there were significantly higher rates of serious AEs with NIVO+IPI combination therapy compared with nivolumab monotherapy.

Economic analysis

6.36 The resubmission presented a cost-analysis, largely based on CA209067, including the cost of managing AEs, drug administration cost and the cost of subsequent therapies over a 3-year time horizon. A threshold analysis was performed to derive the proposed effective price for NIVO+IPI combination therapy, such that the total cost of treating a patient with NIVO+IPI (including subsequent therapies) was equal to the total cost of treating a patient with nivolumab monotherapy.

6.37 The PBAC considered that due to the subsidisation cap currently applying to PD-1 inhibitor monotherapies for melanoma, the cost-analysis, as performed in the resubmission, would not result in zero or negligible financial implications to the Australian Government health budget, and thus was not a cost-minimisation analysis as claimed by the resubmission. The resubmission indicated that the sponsor was unwilling for NIVO+IPI to be included in the current subsidisation cap for PD-1 inhibitor monotherapies for melanoma. In this scenario, the cost offsets resulting from substitution of NIVO+IPI for PD-1 inhibitor monotherapy, as applied in the submission's cost-analysis (and in the financial estimates), would not be realised. The PBAC noted that over the period 1 September 2016 to 31 August 2017, the total

Commonwealth expenditure on PD-1 inhibitor monotherapy for melanoma, before application of the cap, was greater than $100 million , but was capped at $60 - $100 million (i.e. more than [redacted]% of nivolumab monotherapy scripts currently incur no cost to the Government). Therefore, the total cost for PD-1 inhibitor monotherapy for melanoma would remain constant until utilisation of monotherapy dropped below the monotherapy subsidisation cap, and the cost to the PBS for NIVO+IPI would be additional to this. The PBAC and ESC noted that the resubmission requested separate item numbers for nivolumab and ipilimumab when used in combination (NIVO+IPI) from those used to denote the PBS listings for nivolumab monotherapy and ipilimumab monotherapy, to assist with tracking and reconciling the rebate payable to the Commonwealth. The PBAC and ESC considered that the application of nivolumab cost offsets in the cost analysis (and financial analysis) were not appropriate in the scenario of separate subsidisation caps.

6.38 The doses for NIVO+IPI and nivolumab monotherapy were assumed to be the trial-based doses, i.e. the mean number of doses received in the corresponding treatment arms of CA209067 over the 3 years of follow-up. The numbers of doses of NIVO+IPI and nivolumab monotherapy received in CA209067 are presented in the table below.

Table 10: Number of doses received in CA209067 (ITT population)

	NIVO+IPI		Nivolumab monotherapy
No. of doses	**Nivolumab**	**Ipilimumab**	
1	29 (9.3%)	30 (9.6%)	9 (2.9%)
2	59 (18.8%)	60 (19.2%)	8 (2.6%)
3	42 (13.4%)	45 (14.4%)	18 (5.8%)
4	36 (11.5%)	178 (56.9%)	11 (3.5%)
>4	147 (47.0%)	0	267 (85.3%)
N (total)	313 (100.0%)	313 (100.0%)	313 (100.0%)
Mean no. of doses	**20.7 infusions**	**3.2 infusions**	**30.5 infusions**
Induction phase	3.2 infusions	3.2 infusions	NA
Maintenance phase	17.5 infusions	NA	NA

IPI = ipilimumab; ITT = intention to treat; NA = not applicable; NIVO = nivolumab
Note: In the induction phase of CA209067, the mean number of nivolumab doses was 3.21 and the mean number of ipilimumab doses was 3.19 (3. Drug Costs. Appendix 1_Section 3 model_NIVO+IPI_mMEL.xlsm).
Source: Table 60, p130 of the resubmission

6.39 The resubmission included discontinuations in the estimation of the equi-effective doses of NIVO+IPI and nivolumab monotherapy. As a result of the high rate of discontinuations associated with the increased toxicity of NIVO+IPI combination therapy, the duration of therapy with NIVO+IPI applied in the cost-analysis was shorter than the duration of treatment with nivolumab, despite a claim of superiority in terms of PFS. This resulted in higher costs per vial of nivolumab and ipilimumab, when used in combination therapy, than if the duration of treatment had been based on the mean PFS (i.e. the full course of treatment) or if the treatment duration of nivolumab had been assumed to be the same when used in combination and monotherapy. The ESC noted that although it was not explicitly stated in the trial protocol, nearly all patients who discontinued ipilimumab also discontinued nivolumab (see Table 10) and this contributed to the reduced

nivolumab treatment duration in the combination arm compared with the monotherapy arm. Although it is recommended in the PI for nivolumab that if either agent is withheld, the other agent should also be withheld, the ESC considered this is unlikely to reflect how the combination would be used in clinical practice as patients who experience toxicity are likely to discontinue the ipilimumab but remain on the nivolumab. The ESC was concerned that in this scenario, and particularly as the submission proposed a separate item number for nivolumab monotherapy in the continuing phase, the Commonwealth will incur the cost of nivolumab monotherapy (at a higher unit cost); this use is currently [redacted] under the current Risk Share Arrangement (RSA) for nivolumab for utilisation above the agreed annual expenditure caps. This is because, in clinical practice it is likely that the average duration of nivolumab treatment when used in combination with ipilimumab will be substantially longer than observed in the trial and more consistent with that observed for nivolumab monotherapy. The pre-PBAC response did not agree that patients receiving NIVO+IPI would receive equivalent doses to those on nivolumab monotherapy, re-asserting that patients would cease all treatment even if toxicity was related to ipilimumab only. The PBAC considered the duration of nivolumab treatment when used in combination with ipilimumab to be uncertain.

6.40 The results of the cost analysis are summarised below. Updated costs presented in the pre-PBAC response are explained in more detail below (paragraph 6.45 and Figure 1)

Table 11: Cost calculation – Australian adjusted analysis (with consideration of the PD-1 inhibitor subsidisation cap)

Nivolumab monotherapy costs		
Drug cost: nivolumab (estimated capped EMP)	$ [redacted]*	
Additional costs	$ [redacted]**	
Total cost nivolumab monotherapy **(A)**	**$** [redacted]	
Pre-PBAC response (3.2 doses of IPI per patient; 80% of NIVO patients receive IPI 2L, as compared to 95%) **(A†)**	**$** [redacted]	
NIVO+IPI cost off sets		
NIVO+IPI admin costs	$ [redacted]	
NIVO+IPI subsequent therapy drug costs	$ [redacted]	
NIVO+IPI subsequent therapy admin costs	$ [redacted]	
NIVO+IPI AE costs	$ [redacted]	
Total cost offsets **(B)**	$ [redacted]	
Cost-min NIVO+IPI drug costs (A-B) (EMP)	**$** [redacted]	
Pre-PBAC response (A†-B)	**$** [redacted]	
Calculation of prices per vial for NIVO+IPI		
Duration of therapy (infusions)	Induction	3.21
	Maintenance	17.49
Mean dose/infusion (including wastage)[a]	Induction	
	NIVO = 100mg IPI = 250mg	
	Maintenance	
	NIVO = 260mg	
Proposed price per vial (effective EMP)	NIVO 40mg	$ [redacted]
	NIVO 100mg	$ [redacted]
	IPI 50mg	$ [redacted]
	IPI 200mg	$ [redacted]
Total NIVO+IPI drug costs (effective EMP)	Nivolumab: $ [redacted][b] Ipilimumab: $ [redacted][c] **NIVO+IPI: $** [redacted]	

2L = second-line; AE = adverse event; EMP = Ex-manufacturer price; IPI = ipilimumab; NIVO = nivolumab; PBAC = Pharmaceutical Benefits Advisory Committee; PD-1 = programmed cell death 1

* This is calculated assuming a mean body weight of 80.6kg and the number of infusions of 10.96, which was derived from the capped dispensed price per course per patient (see Table 13 for details).

** Costs of administration, managing adverse events and subsequent therapies

[a] Assuming average weight of 80.8 kg.

Note: the resubmission used the average weight of patients in the NIVO+IPI arm of CA209067 to calculate the cost of NIVO+IPI. An average weight of 80.6 kg (the average weight in the nivolumab monotherapy arm of CA209067) was used to calculate the cost of nivolumab monotherapy. This discrepancy did not affect the combination of vials required to supply the mean dose.

[b] Nivolumab: 1 x 100 mg vial x 3.21 infusions (induction) plus (1 x 100 mg vial + 4 x 40 mg vials) x 17.49 infusions (maintenance)

[c] Ipilimumab: (1 x 200 mg vial + 1 x 50 mg vial) x 3.21 infusions

Source: Table 74, p143 of the resubmission

6.41 Based on the calculation presented in the resubmission (and updated in the pre-PBAC response), the estimated cost per course per patient, based on the ex-manufacturer price, for NIVO+IPI would be $[redacted] ($[redacted]) compared with $[redacted] for nivolumab monotherapy. The incremental cost per course for NIVO+IPI compared with nivolumab monotherapy was largely offset by the additional cost associated with ipilimumab monotherapy in patients who have progressed following nivolumab monotherapy. Both the proportion of patients likely to receive ipilimumab subsequent to PD-1 inhibitor monotherapy and the mean number of doses they are likely to receive are uncertain, and therefore the cost offsets from

subsequent therapies in the nivolumab monotherapy arm are subject to substantial uncertainty.

6.42 The PBAC and ESC noted the additional costs associated with NIVO+IPI and nivolumab monotherapy over the 3 year time horizon of the cost analysis in the comparison below (and those presented in the pre-PBAC response).

Table 12: Comparison of additional costs and cost offsets

Cost category	NIVO+IPI	Nivolumab monotherapy	Difference
Admin costs for NIVO+IPI and NIVO monotherapy	$	$	-$
Drug costs: Subsequent therapy	$	$	-$
Admin costs: Subsequent therapy	$	$	$
Adverse event costs	$	$	$
Total costs	**$**	**$**	**-$**
Pre-PBAC response	**$**	**$**	**-$**

IPI = ipilimumab; NIVO = nivolumab; PBAC = Pharmaceutical Benefits Advisory Committee
Source: Table 73, p142 of the resubmission; Excel workbook 'Appendix 1_Section3 model_NIVO+IPI_mMEL.xlsm'

6.43 The PBAC and ESC noted that the majority of cost offsets applied in the cost analysis were due to the cost of subsequent drug therapy, as assumed by the resubmission. As detailed above, this was considered to favour NIVO+IPI.

6.44 The PSCR argued that the use of trial data to inform the economic evaluation, including the proportion of patients likely to receive subsequent therapy and the mean duration of therapy, was reasonable and appropriate. The ESC noted that in the cost analysis presented by the submission, the proportion of patients who were assumed to receive subsequent therapy (45.9%) was based on the trial data. However, the percentage of patients receiving subsequent therapy following progression on nivolumab monotherapy who were assumed to receive ipilimumab (95%) was based on expert opinion. In CA209067, only 61% of patients who received subsequent therapy following nivolumab monotherapy received ipilimumab. In the pre-PBAC response , the sponsor stated that recent analysis of PBS data from the period January 2013 to July 2017, found that 80% of patients sequencing to second-line therapy after a PD-1 monotherapy received ipilimumab.

6.45 It was not clear whether the mean number of doses of ipilimumab, when used subsequent to nivolumab monotherapy (3.2 in the resubmission), was sourced from trial MDX010-020 (Hodi 2010) (as claimed in the main body of the resubmission) or was assumed to be the same as the mean number of doses of ipilimumab received in the NIVO+IPI arm of CA209067 (as indicated in the Excel workbook for Section 3). MDX010-020 assessed the effectiveness of ipilimumab in patients with metastatic melanoma who had relapsed, failed, or were not able to tolerate at least one or more prior treatment regimens (these treatments did not include PD-1 inhibitors), and was of limited applicability to the proposed PBS population. Similarly, the applicability of the mean number of doses of ipilimumab from CA209067, in which it was used as first line therapy in combination with nivolumab, to use as second/third line monotherapy following progression on PD-1 inhibitor monotherapy was also uncertain. The ESC therefore considered that the extent of utilisation of ipilimumab

in patients who have progressed following nivolumab monotherapy was a source of significant uncertainty in the economic analysis and explored the sensitivity of the analysis to the number of ipilimumab doses by reducing it from 3.2 to 1.6. In the pre-PBAC response, it was stated that the dosing of ipilimumab was based on the 3 year trial data from CA209067. It was also noted that in the DUSC utilisation report on medicines for the treatment of melanoma, patients received 68 days of treatment with ipilimumab, second-line after pembrolizumab (dosing is at 21 day intervals, which equates to 3.2 doses, supporting the data from the trial).

6.46 The pre-PBAC response proposed a new cost-analysis, as presented below.

Figure 1: A comparison of cost calculations (July 2018 resubmission; ESC; and pre-PBAC response)

BMS = Bristol Myers Squibb; DUSC = Drug Utilisation Sub-Committee; ESC = Economic Sub-Committee; IPI = ipilimumab; NIVO = nivolumab; PBAC = Pharmaceutical Benefits Advisory Committee
Source: Figure 1, p2 pre-PBAC response

6.47 In deriving the cost of NIVO+IPI, the resubmission has assumed that the average number of doses of both nivolumab and ipilimumab, as part of combination therapy from the trial, is applicable to both patients with BRAF wild type melanoma receiving first line NIVO+IPI and patients with BRAF mutant type melanoma who would receive NIVO+IPI second line following first line therapy with a BRAF±MEK inhibitor. No justification was given for this assumption.

6.48 The ESC noted no explanation was provided in the submission for the distribution of the total cost of NIVO+IPI between nivolumab and ipilimumab. For the combination arm, the cost for 20.7 (3.21 induction and 17.49 maintenance) infusions of nivolumab was $[redacted] ($[redacted] per induction infusion; $[redacted] per maintenance infusion) and for 3.21 infusions of ipilimumab was $[redacted] ($[redacted] per infusion), resulting in a total cost of $[redacted]. For the monotherapy arm, the cost for 30.5 infusions of nivolumab was $[redacted] ($[redacted] per infusion). Although not a matter for PBAC consideration, the distribution of the total cost of NIVO+IPI between nivolumab and ipilimumab potentially has implications for subsidisation caps.

6.49 The ESC further noted that if it is assumed that the number of nivolumab infusions is the same when used in combination and as monotherapy i.e. 30.5 infusions, the total cost of NIVO+IPI would increase by $[redacted] ((30.5-20.7) x $[redacted]+ $[redacted] additional administration costs) to $[redacted] compared with the base case cost of $[redacted].

Drug cost/patient/course: $[redacted] (dispensed effective price)

6.50 The derivation of the cost for NIVO+IPI is presented in the table below. This was compared with an estimated capped dispensed price of $[redacted]/patient/course for nivolumab, which was derived in the resubmission from the original Deed of Agreement for PD-1 inhibitor monotherapy for unresectable Stage III and Stage IV melanoma and the number of patients likely to be treated each year provided to the sponsor for the purposes of determining equivalent pricing between nivolumab monotherapy and pembrolizumab monotherapy. In the previous resubmission, the cost/patient/course of NIVO+IPI was estimated to be $[redacted], compared with $[redacted] for the sequential treatment with nivolumab monotherapy followed by ipilimumab monotherapy upon progression.

Table 13: Derivation of the average effective dispensed price per course per patient for NIVO+IPI

	Ipilimumab	Nivolumab	
		Induction phase	Maintenance phase
Dose per infusion	3 mg/kg	1 mg/kg	3 mg/kg
Mean body weight	80.8 kg	80.8 kg	80.8 kg
Mean dose per infusion	242 mg	81 mg	242 mg
Mean effective cost per infusion			
Ex-manufacturer price	$[redacted][a]	$[redacted][b]	$[redacted][c]
Dispensed price	*$[redacted][d]*	*$[redacted][d]*	*$[redacted][d]*
Number of infusions	3.21	3.21	17.49
DP/course/patient	$[redacted]	$[redacted]	$[redacted]
Total effective dispensed price/course/patient	Nivolumab: *$[redacted]* Ipilimumab: *$[redacted]* **Total: $[redacted]**		

DP = dispensed price; IPI = ipilimumab; NIVO = nivolumab

[a] 1 x 200 mg vial at $[redacted] (ex-manufacturer) and 1 x 50 mg vial at $[redacted] per vial (ex-manufacturer).

[b] 1 x 100 mg vial at $[redacted] per vial (ex-manufacturer)

[c] 1 x 100 mg vial at $[redacted] per vial (ex-manufacturer) and 4 x 40 mg vial at $[redacted] per vial (ex-manufacturer).

[d] *Assuming public:private split of [redacted]%:[redacted]% (as in Section 4 of the resubmission); distribution fee $26.28, diluent fee $5.21, preparation fee $103.83, ready prepared dispensing fee $7.15. Note: the resubmission assumed a public:private split of [redacted]%:[redacted]% in the economic analysis and used a preparation fee of $83.83 in both the economic analysis and the financial estimates.*

Figures in italics were calculated during the evaluation.

Source: Tables 81-83, pp153-4 of the resubmission; Spreadsheet 3c.Impact – EFF,Excel book 'Appendix 2_BIM_NIVO+IPI.xlsm'

Estimated PBS usage & financial implications

6.51 This resubmission was considered by DUSC. The resubmission presented a new financial analysis reflecting the change in the proposed population and the nominated comparator, and using different PBS data to estimate the eligible population from that used in the previous resubmission.

6.52 The resubmission used a mixed epidemiological approach to estimate the eligible population, based on 100% PBS data for patients initiating PBS-subsidised treatment

for first line treatment of unresectable Stage III or Stage IV melanoma (BRAF inhibitors, ipilimumab, PD-1 inhibitor or fotemustine). The proportion of patients assumed to receive each treatment option, at each line of therapy, was based on expert opinion. The PBAC noted that up to 329 patients from a patient access program may transfer to PBS-subsidised NIVO+IPI in Year 1 of listing. Only first and second line therapies were included in the analysis.

6.53 While the use of PBS data was appropriate, the numbers of patients initiating first line treatment over the first six years of listing were projected from a single time point, based on only 6 months of data and were, therefore, subject to some uncertainty. The PBAC considered that the assumed growth rate in the number of patients treated per year of 2% may be an underestimate, given that cancer incidence projections from 2011 to 2020, published by the Australian Institute of Health and Welfare (AIHW), estimated annual growth rates in the incidence of melanoma of between 2.9%-3.7% per year.

6.54 The proportion of patients assumed to receive each treatment option was the major source of uncertainty in the estimation of the number of patients likely to be treated with NIVO+IPI, although these uptake rates had limited impact on the net cost to the PBS/RPBS once offsets of changes in other medicines were taken into account.

6.55 The mean effective price per infusion for each component of NIVO+IPI combination therapy was derived using the methodology outlined in the table above[§], above, while the mean price per infusion of nivolumab monotherapy was derived from the estimated capped cost per patient per course, as in the economic analysis.

6.56 The resubmission assumed that all use of NIVO+IPI (other than in patients transferring from the patient access program) would substitute for use of PD-1 inhibitor monotherapy. As discussed above, the DUSC considered that if NIVO+IPI is subject to a separate subsidisation cap from that currently applied to PD-1 inhibitor monotherapy, the cost offsets resulting from substitution of NIVO+IPI for PD-1 inhibitor monotherapy would not be realised. This would be because the total cost for PD-1 inhibitor monotherapy would remain constant until utilisation of monotherapy dropped below the original subsidisation cap, and the cost to the PBS for NIVO+IPI would be additional to this.

6.57 The estimated use and financial implications of listing NIVO+IPI for the treatment of unresectable Stage III or Stage IV melanoma are summarised below.

[§] In calculating the dispensed price, the resubmission used a preparation fee of $83.83 and a ready prepared dispensing fee of $7.21.

Table 14: Estimated use and financial implications (effective prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of NIVO+IPI						
Number of patients treated	[redacted][a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of infusions[a]						
Induction phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of NIVO+IPI						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for nivolumab monotherapy, ipilimumab monotherapy and chemotherapy						
Cost to PBS/RPBS *Corrected*[c]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]
Copayments *Corrected*[c]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]
Cost to PBS/RPBS less copayments *Corrected*[c]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]
Net financial implications to the Australian Government						
Net cost to PBS/RPBS *Corrected*[c]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]
Net cost to MBS[d]	$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS/MBS ***Corrected***[c]	**$[redacted]** **$[redacted]**	**$[redacted]** **$[redacted]**	**$[redacted]** **$[redacted]**	**$[redacted]** **$[redacted]**	**$[redacted]** **$[redacted]**	**$[redacted]** **$[redacted]**
Net cost to health budget March 2017 resubmission	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

IPI = ipilimumab; MBS = Medicare Benefits Schedule; NIVO = nivolumab; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] Includes 260 patients from the sponsor's patient access program.

[b] Assuming an average of 3.2 doses in the induction phase (combination therapy) and 17.5 doses in the maintenance phase (single agent nivolumab).

[c] *Figures in italics were calculated during the evaluation, assuming 9.33 infusions of fotemustine per patient (10.67 infusions per patient used in the resubmission), and correcting the error in cells K26:P26 of spreadsheet '3c. Impact – EFF, Appendix 2_BIM_NIVO+IPI.xlsx' in which copayments were added to the cost to the RPBS, rather than subtracted.*

[d] Includes costs of infusions for NIVO+IPI, nivolumab monotherapy and ipilimumab monotherapy (MBS items 13918 and 13915).

Note: The considerably higher net cost in Year 1 is due to the inclusion of patients from the sponsor's patient access program (cost offsets due to substitution for nivolumab monotherapy were not applied to these patients).

Source: Table 84, p156, Table 88 p159 and Table 92, p161 of the resubmission; Excel workbook 'Appendix 2_BIM_NIVO+IPI.xlsx'.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than $10 million.

6.58 The PBAC considered that the high net cost to the PBS/RPBS in Year 1 ($20 - $30 million) was likely due to grandfathered patients, noting that there was uncertainty regarding the number of patients. The PBAC considered that the overall financial impact for the estimated less than 10,000 patients per year remained high and was uncertain.

6.59 The DUSC considered that the financial impact estimates presented in the resubmission were underestimated as:

- if NIVO+IPI is not included in the same subsidisation cap as PD-1 inhibitor monotherapies for melanoma, the net cost to the PBS/RPBS would be considerably higher than estimated in the resubmission; and

- cost offsets for medicines displaced by NIVO+IPI were likely to have been overestimated as:
    - the rate of discontinuation from therapy with NIVO+IPI was high, therefore time on combination therapy in practice, and hence the time on displaced medicines, was likely to be less than estimated by the resubmission. The pre-PBAC response disagreed with the DUSC, stating that the recent DUSC review of medicines for the treatment of melanoma found the median time on PBS medication was similar to the PFS times observed in the clinical trials, and that the number of ipilimumab doses second-line reflected that in the pivotal trial. In addition, the pre-PBAC response stated that the duration of subsequent therapy had little impact on the economic results, stating that if this was reduced from the base case of six months to three months, the drug cost for NIVO+IPI increased from $[redacted] to $[redacted]; and
    - the assumption that 43.6% of nivolumab monotherapy patients (i.e. submission proposal in Figure 1) would avoid needing second-line therapy with ipilimumab was high relative to actual PBS use. The DUSC review indicated that around one-fifth (20%) of patients were supplied with ipilimumab second-line. The pre-PBAC response suggested that as the DUSC review followed a cohort of patients for 18 to 24 months, compared to a minimum follow-up of 36 months in CA209067, the proportion of patients who would have progressed onto second-line ipilimumab would be less (i.e. 20% versus 43.6%). In reducing the proportion of patients who receive second-line ipilimumab from 95% to 80% in the cost analysis (i.e. BMS proposal in Figure 1), the proportion of nivolumab monotherapy patients receiving second-line ipilimumab was effectively reduced from 43.6% to 36.7%.

Quality Use of Medicines

6.60 The resubmission did not provide any evidence for the comparative effectiveness of second-line NIVO+IPI versus second-line nivolumab monotherapy in patients with BRAF mutant type melanoma who have progressed following BRAF±MEK inhibitor therapy. DUSC considered that the use of the combination therapy in this setting may result in utilisation without meaningful clinical benefits to patients over PD-1 monotherapy yet expose them to additional harms.

6.61 The PBAC acknowledged that clinicians were becoming better versed in treating the adverse events, particularly in the urban setting, but noted that safety in the more rural and remote settings and private hospitals remained a concern. The PBAC noted that there was a need for improved access to high-cost rescue therapies in these settings, for example infliximab for treatment-induced colitis which is not currently PBS-funded for this indication nor routinely available on hospital formularies.

Financial Management – Risk Sharing Arrangements

6.62 The resubmission stated that the sponsor was willing to consider addressing uncertainty in the financial estimates with a RSA, providing a [redacted]% rebate beyond the agreed subsidisation caps. The sponsor requested a subsidisation cap specifically for NIVO+IPI, based on the financial estimates provided in the budget impact analysis, separate from the subsidisation cap currently applying to PD-1 monotherapies for unresectable Stage III or Stage IV melanoma. The previous resubmission did not propose any specific RSA for NIVO+IPI.

6.63 The ESC considered that this will result in the Commonwealth incurring the costs for nivolumab that are currently rebated under the current RSA for nivolumab (refer to paragraphs 6.37 and 6.39 above).

6.64 The pre-PBAC response stated that as the basis for the cost analysis was cost neutrality over two lines of treatment, expenditure for both PD-1 monotherapy and subsequent therapies, including ipilimumab, needed to be considered when determining the expenditure caps, not just the PD-1 monotherapy expenditure.

The DUSC considered that the request for a separate subsidisation cap for the combination therapy was inconsistent with its proposed listing on a cost-minimisation basis to PD-1 monotherapies. DUSC stated that the suggested arrangements would result in an increased cost to the Commonwealth unless the ceiling on the original cap was reduced to match the amount of costs to be incurred under the newly envisaged cap. That is, for cost neutrality, the sum of the expenditures under the two caps should equate to the expenditure under the original cap. DUSC noted the PSCR stated that it would not be commercially viable for NIVO+IPI to join the existing RSA for PD-1 monotherapy as the subsidisation caps for the existing arrangement were already being breached. The sponsor expressed a willingness to establish a separate subsidisation cap for NIVO+IPI.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required (STREAMLINED) listing of concurrent use of nivolumab and ipilimumab (NIVO+IPI) for the treatment of unresectable Stage III or Stage IV malignant melanoma, as first-line immunotherapy in patients with BRAF V600 mutation negative melanoma, and subsequent to BRAF inhibitor with or without MEK inhibitor therapy in patients with BRAF V600 mutation positive melanoma, on the basis of cost neutrality to the PBS. In making this recommendation, the PBAC considered the high unmet clinical need in an aggressive and debilitating malignancy and advised that NIVO+IPI combination therapy demonstrated superior comparative effectiveness in terms of a gain in progression free survival (PFS) compared to nivolumab monotherapy; however, the adverse event profile compare to nivolumab monotherapy was inferior and the effect on

quality of life (QoL) and overall survival (OS) remained unknown.

7.2 The PBAC noted the input provided by individuals, health care professionals and organisations describing the clinical benefits, the high consumer demand and the incidence, severity and management practices of adverse events.

7.3 In terms of the clinical place in therapy, the PBAC recalled that in previous submissions the requested restriction included all patients with Stage III or IV unresectable metastatic melanoma, irrespective of BRAF status or treatment line. At the March 2017 PBAC meeting the Committee requested that NIVO+IPI be restricted in patients with BRAF mutant melanoma to those who have progressed following treatment with a BRAF±MEK inhibitor, consistent with the current melanoma PBS listings for nivolumab and pembrolizumab monotherapy and the findings of the Pasquali, 2017 network meta-analysis (paragraph 7.2, 7.3 nivolumab plus ipilimumab Public Summary Document (PSD), March 2017 PBAC meeting). The PBAC considered that the proposed PBS restriction was consistent with its request.

7.4 The resubmission again nominated PD-1 inhibitor monotherapy (e.g. nivolumab or pembrolizumab) as the primary comparator for NIVO+IPI. The key trial was again CA209067, in which nivolumab monotherapy was compared to NIVO+IPI. The PBAC recalled that it had previously considered that the CA209067 trial provided the best available data for the comparative effectiveness and safety of NIVO+IPI relative to nivolumab monotherapy in the first-line setting (paragraph 7.4, nivolumab plus ipilimumab PSD, March 2017).

7.5 The PBAC noted the updated clinical data provided from the May 2017 database lock of CA209067. These data, with a minimum follow-up of 36 months, reaffirmed the PBAC's previous conclusion that NIVO+IPI demonstrated a modest improvement in PFS over nivolumab monotherapy. The PBAC considered that the OS data remained immature and showed no statistically significant effect for NIVO+IPI beyond that of nivolumab monotherapy, and there remained no evidence of improved QoL.

7.6 The PBAC noted that the resubmission presented limited updated safety data from the May 2017 database lock of CA209067. The PBAC considered that NIVO+IPI resulted in higher rates of any adverse events compared to nivolumab monotherapy (96% versus 86% respectively at 36 months). The PBAC acknowledged that the adverse events were mostly short-term, but reiterated that there were significantly higher rates of serious adverse events with the combination therapy at nine months, a considerable proportion of which required treatment with immune-modulating medications. The PBAC again considered whether the increased toxicity was balanced by improved clinical benefits, noting the evidence provided by the ESC in March 2017 (Schadendorf, 2016) and during the Sponsor hearing that NIVO+IPI combination patients who discontinued treatment due to adverse events still derived a significant efficacy benefit. The PBAC also specifically considered the consumer group comments from the Melbourne Melanoma Project that noted the toxicity issues with the combination therapy, but stated that clinicians were becoming well versed in dealing with them. The PBAC noted this may be the case in

large metropolitan hospitals which regularly treat patients with NIVO+IPI combination therapy, but noted that safety in the more rural and remote settings and private hospitals remained a concern. The PBAC considered that there was a need for improved access to immune-modulating rescue therapies in these settings, for example infliximab for treatment-induced colitis which are not currently PBS-funded for this indication nor routinely available on hospital formularies.

7.7 The PBAC recalled that the previous submission presented a cost-utility analysis that resulted in an incremental cost-effectiveness ratio (ICER) of more than $200,000 per quality adjusted life year (QALY), which was unacceptably high and uncertain (paragraph 7.7, nivolumab plus ipilimumab PSD, March 2017). The resubmission presented a cost-analysis in which the total cost of treating a patient with NIVO+IPI (including subsequent therapies) was stated to be equal to the cost of treating a patient with nivolumab monotherapy (including subsequent therapies). This cost was then used to derive the proposed effective prices for nivolumab and ipilimumab. The PBAC raised a number of concerns regarding the cost analysis including that:

- the analysis was sensitive to the duration of nivolumab treatment following induction in combination with ipilimumab (17.49 doses) compared to when used as monotherapy (30.5 doses), the proportion of patients who used ipilimumab following nivolumab, and the number of cycles of ipilimumab when used following nivolumab;
- due to the subsidisation cap which currently applies to PD-1 monotherapies for melanoma, the cost-analysis, as performed in the resubmission, would not result in a zero or negligible financial implication to the Australian Government health budget, and was therefore not a cost-minimisation analysis as claimed by the resubmission; and
- the resubmission requested separate items numbers for nivolumab and ipilimumab when used in combination, and therefore the application of nivolumab monotherapy cost offsets in the cost analysis (and the financial analysis) were not appropriate in the scenario of separate subsidisation caps.

7.8 The PBAC recalled that it considered the previous financial estimates to be uncertain and the financial impact to be high at more than $100 million over five years (paragraph 7.8, nivolumab plus ipilimumab PSD, March 2017). The PBAC noted that the resubmission offered considerable price reductions for nivolumab ([redacted]% to [redacted]%) and ipilimumab ([redacted]%). However, the PBAC considered that the financial impact of listing NIVO+IPI on the PBS for the estimated less than 10,000 patients remained high (approximately $60 - $100 million over the first six years) and was likely to be considerably underestimated due to the issues surrounding the subsidisation cap outlined above and as the cost offsets for medicines displaced by NIVO+IPI were likely to have been overestimated.

7.9 The PBAC noted that the resubmission stated that the uncertainty in the cost-analysis and financial estimates could be addressed in a Risk Share Arrangement which provided [redacted]% rebate beyond the currently agreed subsidisation caps. The

sponsor requested a subsidisation cap specifically for NIVO+IPI, which was separate to the caps currently applying to PD-1 monotherapies for unresectable Stage III or Stage IV melanoma. The PBAC recommendation of NIVO+IPI was on the basis of cost neutrality to the PBS, that is, that the total sum of expenditure by the Australian Government for PD-1 inhibitors and ipilimumab would not increase following the listing of NIVO+IPI for unresectable Stage III or Stage IV melanoma. The PBAC agreed with the advice of DUSC and considered that the request for a separate subsidisation cap for the combination therapy as suggested by the sponsor was inconsistent with its proposed listing on a cost-minimisation basis to PD-1 monotherapies.

7.10 The PBAC noted that to achieve a true no-cost listing, the current PD-1 monotherapy cap would have to remain unchanged. The PBAC noted that this approach would be the same should a new drug be recommended for the same indication on a cost-minimisation approach. The PBAC further noted that the ipilimumab financial cap for the treatment of melanoma has never been exceeded and therefore any increase in the current utilisation of ipilimumab due to the change to its listing would result in a cost to the PBS. PBAC therefore considered that it may be appropriate for the current financial caps to be renegotiated to a level consistent with the current numbers of patients accessing ipilimumab through the PBS, allowing for annual incidence.

7.11 The PBAC further noted that it is likely that the potential need for access to rescue therapies, for example infliximab for treatment-induced colitis, may also result in an additional cost to the health system; however, this was difficult to quantify. The PBAC were concerned that listing NIVO+IPI without funded access to rescue therapies such as infliximab raised a safety concern, particularly in rural and remote settings and private hospitals, and requested that the secretariat work with the sponsor to ensure access to rescue therapies is available prior to the listing of NIVO+IPI.

7.12 The PBAC noted that no clinical evidence was provided to support the use of NIVO+IPI combination therapy in patients with and Eastern Cooperative Oncology Group (ECOG) performance status of >1 or with ocular or uveal melanoma and therefore recommended that the listing restrict use to reflect these limitations in clinical evidence.

7.13 The PBAC noted advice from the sponsor that up to 329 additional patients would receive NIVO+IPI via a patient access program. The PBAC recommended that a grandfather arrangement be added to the listing to provide equity of access for those patients who would have met the initial PBS criteria at the time of commencing treatment.

7.14 The PBAC advised that NIVO+IPI combination therapy is not suitable for prescribing by nurse practitioners.

7.15 The PBAC recommended that the Early Supply Rule should not apply to the listing of NIVO+IPI combination therapy.

7.16 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953*

that NIVO+IPI combination therapy should not be treated as interchangeable on an individual patient basis with any other drugs.

7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Extend existing listings as follows:

Induction phase

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Proprietary name and manufacturer	
Induction (combination) phase				
NIVOLUMAB 100 mg/10 mL injection, 1 x 10 mL vial 40 mg/4 mL injection, 1 x 4 mL vial	120 mg	3	Opdivo®	Bristol-Myers 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	Yervoy®	Bristol-Myers Squibb Australia Pty Ltd (BQ)

Requested restriction for patients with BRAF V600 mutation negative melanoma	
Category / Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
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) treatment
Restriction:	☒Streamlined
Clinical criteria:	Patient must be receiving PBS-subsidised nivolumab and ipilimumab concomitantly for this condition, AND Patients must not have received prior treatment with ipilimumab or a PD-1 inhibitor for this condition, AND Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, AND Patients must not have ocular or uveal melanoma, 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 under this restriction, AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks under this restriction.
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.

Requested restriction for patients with BRAF V600 mutation positive melanoma	
Category / Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
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) treatment
Restriction:	☒Streamlined
Clinical criteria:	The condition must be positive for a BRAF mutation, AND The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor), OR Patient must be contraindicated to treatment with a BRAF inhibitor, OR Patient must have developed intolerance to a BRAF inhibitor of a severity necessitating permanent treatment withdrawal, AND Patient must be receiving PBS-subsidised nivolumab and ipilimumab concomitantly for this condition, AND Patients must not have received prior treatment with ipilimumab or a PD-1 inhibitor for this condition, AND Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, AND Patients must not have ocular or uveal melanoma, 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 under this restriction, AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks under this restriction.
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.

Continuing phase

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Proprietary name and manufacturer	
Continuing (single agent nivolumab) phase				
NIVOLUMAB 40 mg/4 mL injection, 1 x 4 mL vial 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	11	Opdivo®	Bristol-Myers Squibb Australia Pty Ltd (BQ)

Category / Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Continuing (single-agent nivolumab) treatment
Restriction:	☒Streamlined

Clinical criteria:	Patient must have previously received PBS-subsidised induction treatment with nivolumab and ipilimumab combination therapy for this condition, AND This drug must be the sole PBS-subsidised treatment for this condition, AND Patient must not have developed disease progression whilst being treated with nivolumab and ipilimumab combination therapy for this condition, 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.

Grandfathered patients, induction phase, nivolumab

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Proprietary name and manufacturer	
Induction (combination) phase				
NIVOLUMAB 100 mg/10 mL injection, 1 x 10 mL vial 40 mg/4 mL injection, 1 x 4 mL vial	120 mg	3	Opdivo®	Bristol-Myers Squibb Australia Pty Ltd (BQ)

Requested restriction for patients with BRAF V600 mutation negative melanoma	
Category / Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
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) treatment – Grandfather patients
Restriction:	☒Streamlined
Clinical criteria:	Patients must have received non-PBS-subsidised treatment with nivolumab for this condition prior to <listing date>, AND The treatment must have been and must continue to be in combination with ipilimumab, AND Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, AND Patients must not have ocular or uveal melanoma, 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 under this restriction, AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks under this restriction.
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.

Requested restriction for patients with BRAF V600 mutation positive melanoma	
Category / Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
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) treatment – Grandfather patients
Restriction:	☒Streamlined
Clinical criteria:	Patients must have received non-PBS-subsidised treatment with nivolumab for this condition prior to <listing date>, AND The treatment must have been and must continue to be in combination with ipilimumab, AND The condition must be positive for a BRAF mutation, AND The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor), OR Patient must be contraindicated to treatment with a BRAF inhibitor, OR Patient must have developed intolerance to a BRAF inhibitor of a severity necessitating permanent treatment withdrawal, AND Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, AND Patients must not have ocular or uveal melanoma, 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 under this restriction, AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks under this restriction.
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.

Grandfather patients, induction phase, ipilimumab

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Proprietary name and manufacturer	
Induction (combination) phase				
IPILIMUMAB 200 mg/40 mL injection, 1 x 40 mL vial 50 mg/10 mL injection, 1 x 10 mL vial	360 mg	3	Yervoy®	Bristol-Myers Squibb Australia Pty Ltd (BQ)

Requested restriction for patients with BRAF V600 mutation negative melanoma	
Category / Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
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) treatment – Grandfather patients
Restriction:	☒Streamlined

Clinical criteria:	Patients must have received non-PBS-subsidised treatment with ipilimumab for this condition prior to <listing date>, AND The treatment must have been and must continue to be in combination with nivolumab, AND Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, AND Patients must not have ocular or uveal melanoma, 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 under this restriction, AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks under this restriction.
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.

Requested restriction for patients with BRAF V600 mutation positive melanoma	
Category / Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
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) treatment – Grandfather patients
Restriction:	☒Streamlined
Clinical criteria:	Patients must have received non-PBS-subsidised treatment with ipilimumab for this condition prior to <listing date>, AND The treatment must have been and must continue to be in combination with nivolumab, AND The condition must be positive for a BRAF mutation, AND The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor), OR Patient must be contraindicated to treatment with a BRAF inhibitor, OR Patient must have developed intolerance to a BRAF inhibitor of a severity necessitating permanent treatment withdrawal, AND Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, AND Patients must not have ocular or uveal melanoma, 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 under this restriction, AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks under this restriction.
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.

Grandfathered patients, continuing phase

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Proprietary name and manufacturer	
Continuing (single agent nivolumab) phase				
NIVOLUMAB 40 mg/4 mL injection, 1 x 4 mL vial 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	11	Opdivo®	Bristol-Myers Squibb Australia Pty Ltd (BQ)

Category / Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Continuing (single-agent nivolumab) treatment
Restriction:	☒Streamlined
Clinical criteria:	Patient must have received non-PBS-subsidised treatment with nivolumab for this condition prior to <listing date>, AND Patient must have previously received induction treatment with nivolumab and ipilimumab combination therapy for this condition, AND This drug must be the sole PBS-subsidised treatment for this condition, AND Patient must not have developed disease progression whilst being treated with nivolumab and ipilimumab combination therapy for this condition, 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.

9 Context for Decision

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

10 Sponsor's Comment

The Sponsor is very pleased that this important treatment option for patients with metastatic melanoma has received a recommendation from the PBAC.