

## 7.09 NIVOLUMAB

### **Injection concentrate for I.V. infusion 40 mg in 4 mL, Injection concentrate for I.V. infusion 100 mg in 10 mL, Opdivo<sup>®</sup>, Bristol-Myers Squibb Australia Pty Ltd**

#### **1 Purpose of Application**

- 1.1 The resubmission requested a Section 100 – Efficient Funding of Chemotherapy program listing for nivolumab monotherapy as adjuvant treatment for completely resected Stage III or completely resected Stage IV melanoma. The first submission was considered by PBAC in July 2018.
- 1.2 The sponsor made a minor submission to the March 2019 PBAC meeting for nivolumab (for melanoma, non-small cell lung cancer, renal cell carcinoma, and squamous cell carcinoma of the head and neck) to amend the current weight-based dosing restrictions to include recent TGA approved changes to allow clinicians choice between weight-based and fixed dosing.
- 1.3 The requested listing was based on a cost utility analysis of nivolumab compared with observation/watch and wait as standard of care (SoC). The key clinical components of the resubmission are summarised in the table below.

**Table 1: Key clinical components**

<b>Component</b>	<b>Description</b>
Population	Patients with completely resected Stage III or IV melanoma
Intervention	Nivolumab 3 mg/kg administered as an IV infusion over 60 minutes Q2W for up to a maximum of 12 months.
Comparator	Observation/Watch and wait as standard of care (SoC) The submission also provided comparisons with near market comparators: Dabrafenib plus trametinib (DAB+TRAM) Pembrolizumab
Outcomes	Recurrence-free survival (RFS) Distant metastases-free survival (DMFS) Overall survival (OS) Safety Quality Adjusted Life Years (QALYs)
Clinical claims	Superior RFS and inferior safety outcomes for patients who receive adjuvant nivolumab compared to those who do not (i.e. placebo as a proxy for observation) Comparable RFS and superior safety outcomes for patients who receive adjuvant nivolumab compared to those who receive DAB+TRAM Comparable RFS and non-inferior safety outcomes for patients who receive adjuvant nivolumab compared to those who receive pembrolizumab

IV = intravenous; Q2W = every two weeks

Source: Table 2, p25 of the resubmission.

## 2 Requested listing

2.1 The requested listings for nivolumab adjuvant therapy are presented below.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount <sup>a</sup>	Proprietary name and manufacturer
NIVOLUMAB 40 mg/4 mL injection, 10 mL vial 100 mg/10 mL injection, 10 mL vial	360 mg	Initial: 8	Public Hospital	Opdivo®
		Continuing: 11	\$7,560.74 (published price) \$ [REDACTED] (effective price)	Bristol Myers Squibb
			Private Hospital \$7,704.62 (published price) \$ [REDACTED] (effective price)	

<sup>a</sup> Does not include the \$20 TGA Licensed Compounder fee

<b>Category/Program:</b>	Section 100 Efficient Funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Stage III or IV melanoma that is completely surgically resected
<b>Treatment phase:</b>	Initial treatment
<b>Restriction level/ Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The patient must have histologically confirmed melanoma that is completely surgically resected; i.e., the patient must have been surgically rendered free of disease with negative margins on resected specimens AND The treatment must be as adjuvant therapy adjunctive to current standard care, AND The patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, AND <del>The patient must not have received prior treatment with a PD-1 inhibitor for this condition,</del> AND The patient must not have uveal melanoma.
<b>Notes:</b>	Complete resection of Stage III disease must be documented on the surgical and pathology reports Complete resection of Stage IV disease with margins negative for disease must be documented on the pathology report.

<b>Treatment phase:</b>	Continuing treatment
<b>Restriction level/ Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must have previously been issued with an authority prescription to receive this drug as adjuvant therapy for this condition AND Patient must not have developed recurrent disease while receiving treatment as adjuvant therapy AND The treatment must not exceed a dose of 3 mg per kg every 2 weeks for a period of 12 months in total (initial plus continuing therapy)

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<b>Treatment phase:</b>	Grandfather treatment
<b>Restriction level/ Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have previously been issued with an authority prescription to receive this drug as adjuvant therapy for this condition<sup>b</sup></p> <p>AND</p> <p>Patient must not have developed recurrent disease while receiving treatment as adjuvant therapy</p> <p>AND</p> <p>The treatment must not exceed a dose of 3 mg per kg every 2 weeks for a period of 12 months in total (initial plus continuing therapy)</p>

<sup>b</sup> This clinical criterion appears incorrect for a grandfathering restriction.

Source: Table 19, 20 & 24, p64, 65 & 68 of the resubmission.

2.2 The proposed changes to the initial restrictions for nivolumab and the BRAF inhibitors for the treatment of unresectable Stage III and Stage IV malignant melanoma are presented below.

<b>Nivolumab</b>	
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial treatment 1
<b>Restriction level/ Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The condition must be positive for a BRAF V600 mutation,</p> <p>AND</p> <p>The condition must have progressed following treatment with a BRAF inhibitor (with or without MEK inhibitor) unless contraindicated or not tolerated according to the TGA approved Product Information,</p> <p>AND</p> <p>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for <del>this condition</del> <i>the treatment of unresectable Stage III or Stage IV malignant melanoma</i>,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>The treatment must not exceed a total of 9 doses at a maximum dose of 3 mg per kg every 2 weeks.</p>

<b>Nivolumab</b>	
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial treatment 2
<b>Restriction level/ Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The condition must be negative for a BRAF V600 mutation,</p> <p>AND</p> <p>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for <del>this condition</del> <i>the treatment of unresectable Stage III or Stage IV malignant melanoma</i>,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>The treatment must not exceed a total of 9 doses at a maximum dose of 3 mg per kg every 2 weeks.</p>

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<b>BRAF inhibitors</b>	
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initiation
<b>Restriction level/ Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The condition must be positive for a BRAF V600 mutation, AND <del>The condition</del> <i>The patient</i> must not have been treated previously with PBS subsidised therapy for unresectable Stage III or Stage IV malignant melanoma,; OR Patient must have developed intolerance to another BRAF inhibitor of a severity necessitating permanent treatment withdrawal, AND Patient must have a WHO performance status of 2 or less.

- 2.3 The sponsor proposed that nivolumab be listed on the PBS as an adjuvant treatment for completely resected Stage III and IV melanoma via a Special Pricing Arrangement (SPA). Although the resubmission proposed a Managed Access Program (MAP), the pre-PBAC response stated that the sponsor was willing to withdraw the proposed MAP and accept a cost-effective price based on the available evidence. The previous submission did not propose a MAP for nivolumab.
- 2.4 There is a Risk Sharing Arrangement (RSA), in the form of annual expenditure caps, in place for the treatment of unresectable Stage III or Stage IV malignant melanoma, which is shared by the sponsors for pembrolizumab and nivolumab. If nivolumab becomes available on the PBS as an adjuvant treatment, this will likely have downstream consequences for the utilisation of the shared caps in the unresectable or metastatic setting (see paragraphs 6.67 and 6.68).
- 2.5 Patients with ocular melanoma were excluded from the nivolumab CA238 trial. The resubmission requested that the clinical criteria exclude use in patients with uveal melanoma but not in patients with ocular melanoma in general, based on consultation with the sponsor’s Advisory Board. The resubmission argued that uveal melanoma is resistant to conventional melanoma treatments, while the term “ocular melanoma” was confusing and may imply that conjunctival melanoma would not be eligible for treatment. The ESC advised that this was reasonable.
- 2.6 The PBS listing for patients with Stage III and IV completely surgically resected melanoma is broader than the evidence presented in the resubmission. When staged using the 7<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) melanoma staging system (see paragraphs 6.9 and 6.10) very limited data was provided for patients with completely resected Stage IIIA melanoma (2/906; 0.4%) and no comparative data were presented for patients with Stage IV melanoma.
- 2.7 The Pre-Sub-Committee Response (PSCR) stated that re-categorisation of patients within Study CA238 using the 8<sup>th</sup> edition of the AJCC system resulted in 4.7% (43/906) of patients with Stage IIIA disease. The PSCR argued that the treatment effect seen for the total population in CA238 was not diminished when Stage IIIA patients were

excluded from the analysis, indicating that the presence of these patients in the sample did not materially change the trial result. The ESC noted similar results would be expected given the exclusion of only 4.7% of patients. The PSCR further argued that Stage IIIA patients may self-select to have no treatment, although it noted that there is evidence (from the nivolumab Patient Access Program (PAP)) of a clinical desire to have adjuvant nivolumab available to this population. The ESC noted that 11% (59/517) of patients in the nivolumab PAP had Stage IIIA disease, higher than expected based on the proportion of Stage III disease that is Stage IIIA in the Australian sample described by Haydu (2017) of 4.8%, suggesting Stage IIIA patients frequently select to have treatment. The ESC advised that there was limited evidence to establish the benefit to risk ratio for Stage IIIA patients.

- 2.8 In terms of the lack of comparative data to support a listing for Stage IV patients, the PSCR argued that these patients are at high risk of metastatic disease, and that excluding these patients would create an illogical treatment gap for patients with a very high need. The ESC advised it would not be appropriate to exclude Stage IV patients from the proposed listing.
- 2.9 Similar to the original submission, the resubmission proposed the use of a programmed cell death-1 (PD-1) inhibitor-containing regimen be allowed in the adjuvant and then in the unresectable or metastatic setting. The resubmission proposed changes to existing nivolumab (and pembrolizumab) listings, and to BRAF inhibitor listings for BRAF mutant patients, which it suggested would provide clarity for prescribers, although it also suggested that the wording of existing listings are sufficient to allow treatment in the adjuvant and then the unresectable or metastatic setting. The PSCR acknowledged there are currently very little data to inform the impact of adjuvant nivolumab treatment on subsequent use of PD-1 inhibitors in the unresectable or metastatic setting, but claimed it was unlikely to negatively impact future treatment. Further, the PSCR highlighted an analysis of data collected on outcomes at the end of the next line treatment which suggested a clinically relevant improvement in PFS for nivolumab versus ipilimumab 10 mg/kg with a hazard ratio (HR) of 0.74 (95% confidence interval (CI): 0.57, 0.97; stratified log-rank p=0.0302). The PBAC agreed that patients who had tolerated and completed the 12 month course of adjuvant nivolumab treatment should be eligible for retreatment with a PD-1 inhibitor for unresectable Stage III or Stage IV disease.
- 2.10 For the adjuvant nivolumab listing, the resubmission requested that the PBAC reconsider its recommendation to exclude patients who had received prior treatment with a PD-1 inhibitor. This would allow patients who experienced a subsequent Stage III or IV melanoma that was fully resected, access to retreatment with adjuvant nivolumab. The sponsor indicated that up to 11% of patients will have a recurrence of resectable disease. The resubmission further proposed that the PBAC could consider excluding from retreatment those patients who developed recurrent disease while receiving adjuvant therapy (i.e. including only patients who develop recurrence post adjuvant therapy). Similar to the previous submission, limited evidence was provided

in the resubmission to support the effectiveness and safety of using nivolumab as retreatment for fully resected Stage III or IV melanoma. The ESC advised that, although not proposed by the submission, patients with unresectable or metastatic disease who respond well to nivolumab therapy, and then go on to have complete resection, may also warrant future access to adjuvant nivolumab therapy. The PBAC noted that no data was presented to support this approach and that patients receiving nivolumab therapy under the Stage IV unresectable listing, who then subsequently undergo surgical resection, may still continue to access nivolumab under the current unresectable listing, if the clinician deems it appropriate to continue treatment. The PBAC did not deem it therefore appropriate, without further data presented, for these patients to access nivolumab under the adjuvant listing, which should be reserved for patients who are naïve to nivolumab therapy.

- 2.11 The resubmission made amendments to the proposed clinical criteria of adjuvant nivolumab (initiation) based on the PBAC's recommendations to include patients with an Eastern Cooperative Oncology group (ECOG) performance status of 0 or 1.
- 2.12 The maximum duration of treatment for adjuvant nivolumab (continuing treatment), was amended to include both the maximum dose (3 mg per kg) and dosing interval (every 2 weeks) as well as maximum duration of treatment (12 months) which is consistent with the PBS listing for nivolumab for unresectable Stage III and Stage IV malignant melanoma. However, the sponsor also made a minor submission to the March 2019 PBAC meeting to request amendments to current weight-based dosing restrictions to include recent TGA approved changes to allow clinicians choice between weight-based and fixed dosing (item 6.14 refers). The TGA recommended dosing is now 3 mg/kg every 2 weeks **or** 240 mg every 2 weeks **or** 480 mg every 4 weeks. The maximum treatment duration for adjuvant melanoma treatment is unchanged at 12 months. The PSCR suggested that the dosing regimen for adjuvant treatment should be aligned with the requested changes to other nivolumab listings, if recommended. The PSCR also indicated that the 480 mg every 4 weeks fixed dosing regimen is likely to be the most utilised regimen for this indication.
- 2.13 The resubmission requested a grandfather listing, noting that since the previous submission, the sponsor had launched a nivolumab PAP for the use of adjuvant treatment in resected Stage III and IV melanoma. As at 16 October 2018, 241 patients had commenced treatment and the resubmission anticipated that 720 patients (i.e. 100% of PAP patients) would be eligible to transition to PBS stock at time of listing.
- 2.14 The ESC noted correspondence from MSAC to the PBAC on 11 February 2019 regarding sentinel lymph node biopsy (SLNB) and the implications for emerging adjuvant therapies. The MSAC noted that clinicians and other stakeholders have advised that all patients diagnosed by SLNB as being Stage IIIA or higher would now be referred to a medical oncologist and multi-disciplinary team to consider whether these patients should be offered systemic adjuvant treatment. The MSAC further noted that, compared to the 7<sup>th</sup> edition of the American Joint Committee on Cancer

(AJCC) melanoma staging system (as used in CA238), the 8<sup>th</sup> edition staging system, which came into effect in Australia in 2018, has changed the proportions of patients classified into the various subcategories of Stage III, and that the risk of melanoma recurrence has also changed across these subcategories (see paragraph 6.9). In particular, more patients are now being classified as having Stage IIIA melanoma, and they may have a lower risk of recurrence than patients with Stage IIIB, IIIC or IIID melanoma. The MSAC asked the PBAC to review the proposed threshold of melanoma staging for the initiation of adjuvant treatment.

- 2.15 The MSAC also advised that the second Multicenter Selective Lymphadenectomy Trial (MSLT-II) demonstrated no improvement in 10-year survival with complete lymph node dissection (CLND) versus nodal observation in patients with a tumour-positive sentinel lymph node (Faries et al, 2017)\*. As a result, some patients with a positive sentinel lymph node may no longer go on to an immediate CLND. This means that some patients will present for treatment with residual microscopically positive regional lymph nodes, whereas in the past (and in the CA238 trial) this group would have undergone CLND.
- 2.16 In relation to the patient population, the PBAC foreshadowed that a recommended PBS listing of adjuvant nivolumab should be limited to patients with completely resected Stage IIIB, IIIC, IIID and Stage IV disease and that it should exclude patients with Stage IIIA disease. This was on the basis of:
- Patients with Stage IIIA disease being excluded from the CA238 trial.
  - Patients with Stage IIIA disease (classified using the 8<sup>th</sup> edition of the AJCC melanoma staging system) have a relatively low risk of recurrence and a five year melanoma-specific survival rate of 93% (see paragraph 6.9).
  - Patients with Stage IIIA disease may now only have had sentinel lymph node biopsy demonstrating microscopic involvement, and the efficacy of nivolumab in these patients was unknown.

The PBAC acknowledged that excluding Stage IIIA disease from adjuvant treatment may encourage immediate CLND as this enables improved staging. However, it was noted in the immediate CLND arm of the MSLT-II trial that non-sentinel node metastases were detected on pathological assessment in only 11.5% patients, and that CLND led to a change in disease stage in less than 6% of patients\*†.

- 2.17 The PBAC noted that, at 5 years in the nodal observation arm of the MSLT-II trial, 26.1% of patients had disease in non-sentinel nodes on the basis of ultrasonographic or physical examination, and this was statistically significantly higher than for the

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\* Faires MB, Thompson JF, Cochran AJ, et al. Complete dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med.* 2017; 376: 2211-2222.

† Madu MF, Franke V, Bruin MM, et al. Immediate completion lymph node dissection in stage IIIA melanoma does not provide significant additional staging information beyond EORTC SN tumour biopsy criteria. *Eur J Cancer.* 2017; 87: 215-215.

immediate CLND arm (19.9%,  $p=0.005$ ). The PBAC considered patients classified as having Stage IIIA disease at the time of excision of the primary tumour, and hence not eligible for adjuvant treatment, should be eligible for adjuvant treatment if and when they meet the criteria for Stage IIIB, IIIC or IIID disease and undergo a salvage nodal resection. The PBAC noted that the proposed PBS criteria did not require patients to commence adjuvant treatment within a certain period following complete resection and advised that commencement within 12 weeks would be reasonable.

- 2.18 Regarding PBS eligibility for patients who have not undergone CLND, noting that CLND was no longer standard of care for all patients with a positive sentinel lymph node, the PBAC considered that “completely resected disease” would, in practice, include all patients with a wide excision of the primary tumour and either CLND or sentinel lymph node biopsy (or both). However, it is currently unknown what proportion of patients will forgo a CLND as, although an improvement in melanoma-specific survival with immediate CLND dissection was not demonstrated in the MSLT-II trial, immediate CLND did increase the rate of regional disease control and provided prognostic information in terms of disease in non-sentinel nodes. The PBAC further noted the value of CLND is currently being debated in the clinical literature, and that immediate CLND is standard of care for patients presenting with clinically positive lymph nodes, and therefore more likely to be undertaken in patients with Stage IIIB, IIIC or IIID or Stage IV disease.

*For more detail on PBAC’s view, see Section 7 PBAC outcome.*

### **3 Background**

#### ***Registration status***

- 3.1 Nivolumab monotherapy was TGA registered in April 2018 for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.
- 3.2 Nivolumab as monotherapy and in combination with ipilimumab has also been TGA approved for the treatment of patients with unresectable or metastatic melanoma.

#### ***Previous PBAC considerations***

- 3.3 The previous submission was considered by PBAC in July 2018, and it also requested PBS listing for nivolumab as an adjuvant treatment for completely resected Stage III and completely resected Stage IV melanoma.
- 3.4 The PBAC decided not to recommend a PBS listing for nivolumab in July 2018. Table 2 below summarises the key outstanding matters from the previous PBAC consideration and how the resubmission addressed those concerns.

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Table 2: Summary of outstanding matters of concern

Matter of concern	How the resubmission addresses it
<p><b>Clinical Issues</b></p> <p>[Paragraph 7.2, July 2018 PSD] If nivolumab becomes available for use as adjuvant therapy, it would likely alter the use of PD-1 inhibitors in the unresectable setting.</p> <p>[Paragraph 4.6, July 2018 PSD] The impact of using nivolumab as adjuvant therapy on the effectiveness and safety of PD-1 inhibitors to treat unresectable disease in patients who experience recurrence is unknown.</p> <p>[Paragraph 2.2, July 2018 PSD] The PBAC and ESC advised that there should be included a criterion that patients must not have received prior treatment with a PD-1 inhibitor for this condition in the initial treatment restriction.</p>	<p>The resubmission proposed clinical management algorithms for the treatment of unresectable Stage III and IV melanoma, subsequent to the proposed PBS listing of nivolumab adjuvant treatment, based on responses to a treatment survey by oncologists.</p> <p>No new clinical trial evidence on the impact of re-treatment on patient health outcomes was presented, so this concern remains outstanding.</p> <p>The resubmission requested that the PBAC reconsider this advice and has allowed for retreatment with a PD-1 inhibitor in the proposed restrictions for patients with completely resected or unresectable melanoma. No clinical trial evidence was presented to support this request. This issue remains outstanding.</p>
<p>[Paragraph 7.3, July 2018 PSD] The applicability of the clinical evidence to the requested patient population was questionable. No evidence for the effectiveness of nivolumab in patients with completely resected Stage IIIA melanoma, and no comparative data for patients with completely resected Stage IIIA or IV melanoma were presented.</p>	<p>The resubmission provided an analysis to show that the distribution of patients across the Stage III sub-stages receiving nivolumab in the clinical trials (CA238 and CA029) was similar after the trial population were re-categorised according to the 8<sup>th</sup> edition AJCC criteria. This distribution across sub-stages was also similar to that seen across the Australian<sup>a,b</sup> patient population (Haydu 2017 and nivolumab PAP). The applicability of the clinical evidence regarding low risk patients (such as those with Stage IIIA) remains a concern. For Stage IV disease, the magnitude of comparative benefit for nivolumab vs. placebo remains uncertain.</p>
<p>[Paragraph 7.4, July 2018 PSD] The PBAC noted that the submission did not assess the proportional hazard assumption in either of the trials.</p>	<p>For trial CA238, the resubmission noted that results of a two-sided Wald Chi-square test in both the 18-month and 24-month follow-ups which suggested the assumption was reasonable (p-value 0.5210 and 0.7881 respectively).</p>
<p>[Paragraph 7.3, July 2018 PSD] The PBAC considered that there were a number of transitivity issues between the trials, including duration of follow-up, maturity of the data, average age of the patients and duration of ipilimumab treatment.</p>	<p><u>Duration of follow-up</u> – CA238 (NIVO vs. IPI) minimum 24 months vs CA029 (IPI vs. placebo) median 2.7 years. The updated data for CA238 with 24 months follow-up indicated that the treatment effect had remained consistent over the additional 6 month data collection period.</p> <p><u>Melanoma types</u> – CA238 all melanoma other than ocular/uveal vs CA029 cutaneous melanoma (excluded mucosal and ocular melanoma or melanoma with unknown origin of the primary).</p> <p><u>Disease stage prior to resection</u> – CA238 Stage IIIB, IIIC and IV (7<sup>th</sup> edition) vs CA029 Stage IIIA, IIIB and IIIC (6<sup>th</sup> edition).</p> <p><u>Duration of treatment</u> – CA238 maximum 12 months vs CA029 maximum of 3 years and doses received in ipilimumab arm CA238 (mean (SD) 4.1 (1.8)) versus CA029 (mean (SD) 5.7 (4.3)). The lower exposure to ipilimumab in the common reference arm in CA238 compared with CA029 potentially favours nivolumab over placebo</p> <p><u>Age ≥ 65 years</u> – CA238 25.8% vs CA029 17.6%. The subgroup analyses indicated there was no statistically</p>

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Matter of concern	How the resubmission addresses it
	<p>significant difference in treatment effect, by age. However the HR for placebo versus ipilimumab indicated treatment effect modification with patients aged <math>\geq 65</math> years having an HR of 1.09 (95% CI: 0.74, 1.61; N = 167), compared with a HR of 1.37 (95% CI: 1.12, 1.64; N = 784) in those aged &lt; 65 years.</p> <p>Uncertainty remains regarding the transitivity and applicability of the trials used in the indirect treatment comparison.</p>
<b>Economic issues</b>	
<p>[Paragraph 7.6, July 2018 PSD] The PBAC considered that the ICER presented in the submission was uncertain, highly variable and likely underestimated. The PBAC raised a number of concerns, including:</p>	
<p>[Paragraphs 6.38 to 6.40, July 2018 PSD] The assumption that the RFS HR derived from the indirect comparison was a surrogate for the OS HR.</p>	<p>The RFS to OS surrogate relationship was no longer applied in the model. The improvement in OS with nivolumab versus placebo was assumed to be the same as for ipilimumab versus placebo.</p>
<p>[Paragraph 6.51, July 2018 PSD] The application of static costs and utilities to each health state which would not accurately reflect the outcome of patients treated in the adjuvant setting over the time horizon of the model (30 years) as recurrence after adjuvant treatment could include a heterogeneous population.</p>	<p>The disease recurrence health state is split into two health states, patients with locoregional recurrence and patients with distant metastatic recurrence. This was done through the introduction of the DMFS curve resulting in 4 health states, as opposed to 3 in the previous model.</p>
<p>[Paragraphs 6.42 and 6.43, July 2018 PSD] The population in the model which was based on CA029 (mean age of 51 years, Stage III patients only) was not applicable to the proposed patient population (mean age at diagnosis of 63 years, Stage III and Stage IV patients).</p>	<p>OS in the revised model is comprised of melanoma-specific mortality (Haydu 2017), and age specific background mortality (Australian life tables). Patient demographics from Haydu (2017) are now applied in the economic model. See comments below (paragraph 6.43 regarding the applicability of this data source to the proposed PBS population.</p>
<p>[Paragraph 6.44, July 2018 PSD] The ESC further noted that adjusting the population age in the model is unlikely to reflect the cost-effectiveness of adjuvant melanoma in a population of patients with an average age of 63 years because adjusting the age does not impact the RFS curve, which was assumed to have a constant hazard from year 5 to 15, and that the curve remained constant after year 15.</p>	<p>Age continues to have no impact on the RFS curve. As described above, the economic model uses age adjusted OS data.</p>
<p>[Paragraph 6.44, July 2018 PSD] Melanoma-specific survival curve was taken from Balch, (2009). No information on the patient baseline characteristics were presented in the publication. Therefore the applicability of this data source was uncertain.</p>	<p>Balch (2009) has been replaced with Haydu (2017). Haydu (2017) reports on clinicopathologic data collected from the Melanoma Institute Australia (MIA) research database, including 4,540 patients with locoregional metastasis and no concurrent or prior diagnosis of distant metastasis. This Australian study does provide baseline characteristics and is expected to be representative of the Australian population. The baseline characteristics from Haydu (2017) are now applied in the model, namely; age (59 years) and sex (40% female). Haydu (2017) included patients (with resected and unresectable disease) from a single Australian institution between 1970 and 2013.</p>

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Matter of concern	How the resubmission addresses it
	There are applicability concerns regarding this cohort to the proposed PBS population (see paragraph 6.43).
[Paragraph 6.44, July 2018 PSD] The competing risk of death due to other causes will not be accurately captured in either the RFS or OS curves.	See response to PBAC minute 6.45 below.
[Paragraph 6.45, July 2018 PSD] The submission stated that the RFS curve for years 5 to 15 for the observation arm was based on an exponential extrapolation of the KM curve of the placebo arm of CA184029. The submission did not explore other methods of extrapolation, nor justify the selection of this method.	A range of parametric survival curves have been fitted to the KM data using DataFit software. Placebo RFS and DMFS curves from CA029 are extrapolated based on 5 years of data. Survival curve from Haydu (2017) is extrapolated based on 15 years of data.  While the resubmission has provided extrapolations based on the usual range of parametric survival curves, concerns remain regarding the applicability of the underlying data sources.
[Paragraph 6.46, July 2018 PSD] The application of a constant transition probability for recurrence-free survival does not incorporate the increasing competing risk of death from other causes such as patients' age. This may overestimate the life years gained from treatment with nivolumab compared to observation.	Death from other causes is now accounted for through the combination of age specific background mortality (Australian life tables) and melanoma specific survival from Haydu (2017).
[Paragraph 6.47, July 2018 PSD] From year 15, the submission assumed that patients were no longer at risk of recurrence. Since the model did not allow patients to transit from recurrence-free to death state, this assumption resulted in the impossible scenario that, patients who remained recurrence-free at year 15 would no longer faced the risk of dying. This is implausible and biased the results of the model in favour of nivolumab.	During the latter years of the extrapolation, the per-cycle hazard of dying from all-cause mortality (which is only captured in the OS curve) is greater than the per-cycle hazard of recurrence or death (represented by the RFS curve). This implied that those patients who are recurrence-free during this time have a better survival than the general population. This is inappropriate.
<b>Financial Issues</b>	
[Paragraph 6.60, July 2018 PSD] The PBAC considered that the size of the eligible patient population was uncertain. Key assumptions included the incidence of melanoma and disease stage.  [Paragraph 7.2, July 2018 PSD] The submission did not fully capture the treatment pathways for patients who would have recurrence of disease and the downstream consequences of PD-1 inhibitor therapy in the unresectable malignant melanoma setting.	The resubmission used a new data source to determine the size of the treatable population and included patients diagnosed with Stage I/II disease that subsequently progress to completely resected Stage III/IV melanoma. This is the one of the main financial uncertainties. The size of the patient population diagnosed with earlier stages of disease that subsequently progress to later stages was estimated on the basis of an outdated published study (Turner 2011, involving patients first diagnosed with stage I or II melanoma in 1985-2009).
[Paragraph 6.63, July 2018 PSD] The PBAC and DUSC considered that the cost offsets were overestimated. Key issues were: <ul style="list-style-type: none"> <li>• the estimated cost offsets in the metastatic setting are likely to be overestimated;</li> <li>• the proposed PBS restriction is broader than the eligibility criteria for the CA238 and CA029 trials; and</li> <li>• uptake is likely to be very high overall, but low in patients who have a good prognosis from resection alone (such as patients with Stage IIIA disease) and in older patients.</li> </ul>	Cost offsets have been revised based on feedback from Australian clinicians and taking into account current expenditure caps in the unresectable malignant melanoma setting. The estimated overall reduction in utilisation of PBS medicines in the unresectable malignant melanoma setting was based on the proportion of current patients that would have been eligible for adjuvant therapy (58%) and the estimated proportion of patients treated with adjuvant therapy prevented from progressing to Stage IV disease (11.1%) as per the economic model. The submission's approach was not well justified in terms of the use of DMFS as a proxy for the avoidance of

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Matter of concern	How the resubmission addresses it
	subsequent treatments for unresectable Stage III or Stage IV melanoma. The change of current RSA caps for treatments in the unresectable setting due to the listing of adjuvant nivolumab is unknown. In addition, the use of the RSA cap in the financial analysis has overestimated the actual government expenditure for ipilimumab.
<p>[Paragraph 7.7, July 2018 PSD]</p> <p>The PBAC considered that although the financial estimates were uncertain, the financial impact was very high (over more than \$100 million per year for less than 10,000 patients per year). This was particularly concerning in the context of the uncertain estimate of cost-effectiveness.</p>	

AJCC = American Joint Committee on Cancer; DMFS = distant metastasis-free survival; DUSC = Drug Utilisation Sub-Committee; ECOG = Eastern Cooperative Oncology Group; ESC = Economic Sub-Committee; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; KM = Kaplan Meier; IPI = ipilimumab; MAP = Managed Access Program; N = total patients in the group; NIVO = nivolumab; OS = overall survival; PAP = patient access program; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PD-1 = programmed cell death 1; PSD = Public Summary Document; RFS = recurrence free survival; RSA = Risk Sharing Arrangement; SD = standard deviation

<sup>a</sup> Presented data from a study by Haydu et al. Conditional Survival: An Assessment of the Prognosis of Patients at Time Points After Initial Diagnosis and Treatment of Locoregional Melanoma Metastasis. *J Clin Oncol.* 2017; 35(15):1721-9.

<sup>b</sup> Presented data from nivolumab patient access program (NIVO PAP).

Source: Table constructed during the evaluation.

For more detail on PBAC’s view, see Section 7 PBAC outcome.

## 4 Population and disease

- 4.1 Melanoma occurs in Australia at eleven times the worldwide rate (35 versus three incident cases per 100,000). In 2016 over 13,000 Australians were diagnosed with melanoma and 1,770 died from the condition. The overall rate of melanoma has increased from 27 cases per 100,000 in 1982 to 49 per 100,000 in 2016, and the mortality rate has risen from 4.7 deaths per 100,000 to an estimated 6.2 deaths per 100,000.<sup>‡</sup>
- 4.2 Based on the 8<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC)<sup>§</sup>, the 5-year melanoma-specific survival (MSS) rate according to Stage III subgroups ranged from 93% in patients with Stage IIIA melanoma to 32% for those with Stage IIID melanoma. The resubmission stated that this information was based on an analysis of data from 43,792 people; of which 40% were patients from Australian centres.
- 4.3 The proposed place for nivolumab is adjuvant treatment, following completely surgically resected Stage III and IV melanoma. While both Australian and international clinical practice guidelines recommend systemic adjuvant treatment of melanoma

<sup>‡</sup> Australian Institute of Health and Welfare. Skin cancer in Australia. 2017; Available from <https://www.aihw.gov.au/reports/cancer/skin-cancer-in-australia/summary>.

<sup>§</sup> Gershenwald et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA: A Cancer Journal for Clinicians.* 2017; 67(6):472-92.

(including with nivolumab) there are currently no PBS-listed systemic treatments available in Australia.

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

## 5 Comparator

- 5.1 The resubmission again nominated observation as standard of care as the main comparator. This ESC considered that this was reasonable.
- 5.2 The resubmission again also nominated dabrafenib plus trametinib (DAB+TRAM) and pembrolizumab as near market comparators.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the classification and staging of melanoma, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (67), health care professionals (8) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with nivolumab as an adjuvant treatment for completely resected Stage III or Stage IV melanoma including prolonged life, improved quality of life and few side effects.
- 6.3 The PBAC noted the correspondence received from Melanoma Patients Australia Limited and the Australian Melanoma Consumer Alliance supporting access to nivolumab as an adjuvant melanoma treatment and the high clinical need.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the nivolumab as an adjuvant treatment for completely resected Stage III or Stage IV melanoma submission, categorising it as one of the therapies of 'highest priority for PBS listing' on the basis of the CA238 phase 3 trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nivolumab, which was a Grade A (out of C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies which is the highest possible grade and restricted to new curative treatments), based on a comparison with ipilimumab in the CA209238 trial.\*\*

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\*\* Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology*

***Clinical trials***

- 6.5 The evidence in the resubmission was again based on an indirect comparison between nivolumab and placebo, with ipilimumab as the common reference:
- CA238: A randomised, double-blind trial comparing nivolumab (N = 453) versus ipilimumab (N = 453) as adjuvant treatment in patients with complete resection of Stage IIIB/C or Stage IV melanoma (all melanoma subtypes other than ocular melanoma). An additional six months of updated RFS data from this trial were provided in the resubmission; and
  - CA029: A randomised double-blind trial comparing ipilimumab (N = 475) versus placebo (N = 476) as adjuvant treatment in patients with complete resection of Stage III cutaneous melanoma. No updated data from this trial were provided in the resubmission.
- 6.6 Details of the CA238 and CA029 trials are provided in Table 3.

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Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Report/Publication citation
CA238	<p>Interim Clinical Study Report for Study CA209238: A phase 3, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab after complete resection of Stage IIIB/C or Stage IV melanoma in subjects who are at high-risk for recurrence (Data cut-off for interim report in previous submission: 15 May 2017).</p> <p>6 months updated data from the original submission: Addendum 1 to the Interim Clinical Study Report for Study CA209238 (Data cut-off for updated results in resubmission: 7 November 2017 (additional 6 months of follow-up - minimum follow-up ~ 24 months).</p> <p>Weber J, Mandala M, Del Vecchio M, Gogas HJ, et al. Adjuvant nivolumab versus ipilimumab in resected Stage III or IV melanoma.</p>	<p>July 2017</p> <p>July 2018</p> <p><i>New England Journal of Medicine</i> 2017; 377(19):1824-35.</p>
CA029	<p>Adjuvant immunotherapy with anti-CTLA-4 monoclonal antibody (ipilimumab) versus placebo after complete resection of high-risk Stage III melanoma: a randomized, double-blind phase 3 trial of the EORTC Melanoma Group.</p> <p>Eggermont AM, Chiarion-Sileni V, Grob JJ, Drummer R, Wolchok JD, Schmidt H, et al. Ipilimumab versus placebo after complete resection of Stage III melanoma: Initial efficacy and safety results from the EORTC 18071 phase III trial. [Conference abstract].</p> <p>Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk Stage III melanoma (EORTC 18071): A randomised, double-blind, phase 3 trial.</p> <p>Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in Stage III melanoma with ipilimumab adjuvant therapy.</p> <p>Coens C, Suci S, Chiarion-Sileni V, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk Stage III melanoma (EORTC 18071): secondary outcomes of a multi-national, randomised, double-blind, phase 3 trial.</p> <p>Coens C, Suci S, Chiarion-Sileni V, et al. Phase III trial (EORTC 18071/CA184029) of postoperative adjuvant ipilimumab compared to placebo in patients with resected Stage III cutaneous melanoma: Health-related quality of life (HRQoL) results. [Conference abstract].</p>	<p>June 2014</p> <p><i>Journal of Clinical Oncology</i> 2014b; 32(15).</p> <p><i>The Lancet Oncology</i> 2015; 16(5):522-30.</p> <p><i>New England Journal of Medicine</i> 2016; 375(19):1845-55.</p> <p><i>The Lancet Oncology</i> 2017; 18(3):393-403.</p> <p><i>Pigment Cell and Melanoma Research</i> 2014;27(6):1181-2</p>

Source: Table 28, pp85-87 of the resubmission.

6.7 The key features of the CA238 and CA029 trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Nivolumab vs. ipilimumab</b>						
CA238	906	R, DB Mean duration of treatment: NIVO: 19.6 doses (SD 7.94) IPI: 4.1 doses (SD 1.84) Minimum FU of 24 months	Low	Stage IIIB/C or Stage IV melanoma that is completely resected <sup>b</sup>	RFS, DMFS, QoL, AEs	Used
<b>Placebo vs. ipilimumab</b>						
CA029	951	R, DB Mean duration of treatment: IPI: 5.7 doses (SD 4.32) PBO: 8.8 doses (SD 4.85) Median FU: 2.7 years (RFS) 5.3 years (OS) <sup>a</sup>	Low	Stage III cutaneous melanoma that is completely resected <sup>b</sup>	RFS, DMFS, OS, QoL, AEs	Used

AE = adverse event; AJCC = American Joint Committee on Cancer; DB = double blind; DMFS = distant metastases free survival; FU = follow up; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PBO = placebo; QoL = quality of life; R = randomised; RFS = recurrence-free survival; SD = standard deviation

<sup>a</sup> The median follow-up for recurrence-free survival in the ipilimumab arm was 2.6 years and in placebo arm was 2.76 years. The median follow-up for OS is 5.3 years in ipilimumab arm and 5.4 years in placebo arm.

<sup>b</sup> Based on the 7<sup>th</sup> edition of AJCC staging manual

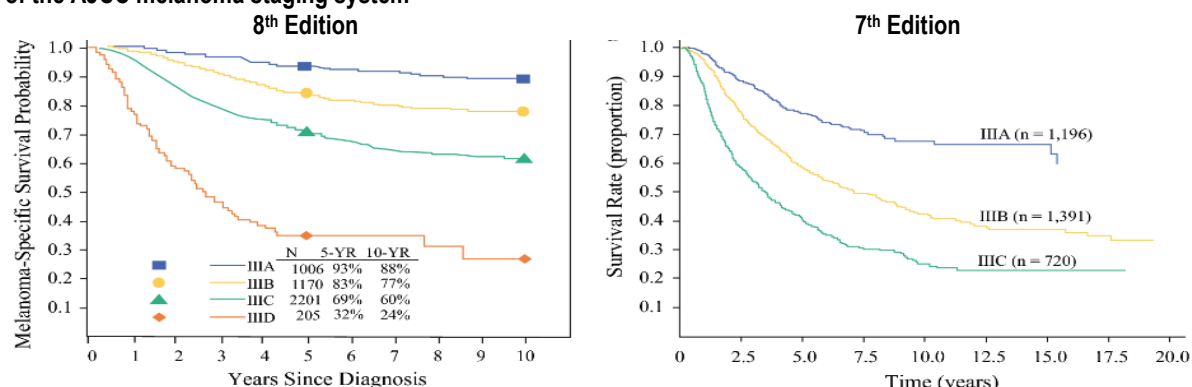
<sup>c</sup> Based on the 6<sup>th</sup> edition of AJCC staging manual

Source: Compiled during the evaluation based on Sections 2 and 3 of the resubmission.

6.8 Patients in CA238 were classified using the 7<sup>th</sup> edition of the AJCC melanoma staging system, which has three prognostic sub-stages, Stages IIIA, IIIB and IIIC, depending upon the extent of lymphatic involvement and the characteristics of the primary tumour. Since 2018, the 8<sup>th</sup> edition of the AJCC Cancer staging system<sup>††</sup> has been used to classify melanoma patients in Australia which subdivides patients into four prognostic sub-stages, Stages IIIA, IIIB, IIIC and IIID. Figure 1 presents a comparison of survival probabilities for each sub-stage of Stage III melanoma using the 7<sup>th</sup> and 8<sup>th</sup> editions of the AJCC staging system.

<sup>††</sup> Gershenwald JE, Scolyer RA, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA: A Cancer Journal for Clinicians*. 2017; 67(6):472-92.

Figure 1: Comparison of survival probability for melanoma using the 7<sup>th</sup> (RIGHT panel) and 8<sup>th</sup> (LEFT panel) editions of the AJCC melanoma staging system



AJCC = American Joint Committee on Cancer; YR = year

Source: Gershenwald JE, Scolyer RA. Melanoma Staging: American Joint Committee on Cancer (AJCC) 8<sup>th</sup> edition and beyond. *Annals of Surgical Oncology*. 2018; 25(8): 2105-2110.

- 6.9 The above comparison suggested that patients in the 8<sup>th</sup> edition cohort had a more favourable survival profile across Stages IIIA, IIIB, and IIIC disease compared with patients with similar stage groupings in the 7<sup>th</sup> edition. It should be noted that the two survival curves were based on populations with substantially different prognostic profiles. Gershenwald (2018) noted that patients included in the 8<sup>th</sup> edition analyses were diagnosed since 1988, whereas the 7<sup>th</sup> edition analyses included patients diagnosed in the 1960s. The better disease-specific survival from the 8<sup>th</sup> edition may be explained by the evolution of surgery, medicine, pathology and nuclear medicine. Additionally, the more recent development of post-recurrence therapies for unresectable or metastatic melanoma (e.g. PD-1 inhibitors and targeted therapies) may mean that the stage-specific survival data presented in the 8<sup>th</sup> edition were not applicable to the proposed PBS population or to the trial patients. Nonetheless, the ESC noted that Stage III disease is associated with heterogeneous outcomes; five-year melanoma-specific survival rates range from 93% for Stage IIIA disease to 32% for Stage IIID disease (8<sup>th</sup> edition), and that the distribution of patients across the subcategories in clinical practice may be different to that in CA238. In particular, use of nivolumab in a higher proportion of lower risk Stage IIIA patients would result in nivolumab being less cost-effective.
- 6.10 No overall survival (OS) data were presented in the resubmission. The resubmission reproduced similar arguments as in the previous submission, regarding RFS as a surrogate for OS (although the RFS to OS surrogate relationship was no longer applied in the economic model). OS remains the most clinically appropriate endpoint that would capture the “overall clinical benefit” associated with adjuvant nivolumab therapy in the completely resected curative setting. The ESC advised that DMFS may be more closely related to OS than RFS, although subject to similar levels of uncertainty in the absence of OS data.

- 6.11 The resubmission argued that previous PBAC concerns regarding transitivity and applicability issues across the CA238 and CA029 trials (see Table 2), including duration of follow-up, maturity of the data, average age of the patients and duration of ipilimumab treatment, were unlikely to impact the indirect comparison results as there was:
- no evidence of effect modification (statistically significant hazard ratios (HR)) by disease sub-stage,
  - overlap of the ipilimumab RFS curves between the trials, and
  - the results of the Wald's test supporting the proportional hazards assumption.
- 6.12 To explore the issue of the different durations of ipilimumab across the trials, an additional indirect treatment comparison (ITC) was presented in the PSCR, which censored patients who received more than 12 months of treatment in the ipilimumab arm of CA029. The indirect treatment effect for RFS was estimated to be HR 0.57 (95% CI 0.44, 0.74). This compared with HR 0.50 (95% CI: 0.38, 0.65) without the censoring applied. The ESC noted that based on the point estimates, the longer duration of ipilimumab in CA029 may have biased the ITC in favour of nivolumab.
- 6.13 The two trials used in the indirect comparison were conducted at different time points (initiation of the CA029 trial was approximately seven years before CA238). It would be expected that the standard of surgical and pathological management of resectable disease would improve with time, as has been observed in Australian clinical practice (Haydu, 2017). This raised the following concerns: 1) the likelihood that patients enrolled in CA238 may have had a lower risk of disease recurrence, after resection, compared to patients in CA029, and 2) the applicability of the CA029 placebo arm to current Australian clinical practice.
- 6.14 In summary, the resubmission presented a non-randomised comparison between two trials with patients who have varying prognosis. The ESC considered the synthesised indirect HR to be unreliable given the noted transitivity issues. The ESC further noted RFS and DFMS are composite outcomes and the results for the components were not compared across the trials.

### ***Comparative effectiveness***

- 6.15 Table 5 summarises the indirect comparison results for the primary outcome, RFS.

**Table 5: Results of the indirect comparison of RFS with updated data from CA238 (nivolumab versus placebo)**

	CA238 ITT: Stage IIIB, IIIC or IV 7 <sup>th</sup> AJCC edition.		CA029 Stage IIIA, IIIB, IIIC 6 <sup>th</sup> AJCC edition	
	Nivolumab N = 453	Ipilimumab N = 453	Ipilimumab N = 475	Placebo N = 476
Follow-up	Minimum 24 months		Median 2.7 years	
Events, n (%)	171 (37.7%)	221 (48.8%)	234 (49.3%)	294 (61.8%)
Median RFS, months (95% CI)	30.75 (30.75, NC)	24.08 (16.56, NC)	26.1 (19.3, 39.3)	17.1 (13.4, 21.6)
p-value (log-rank test)	<b>&lt; 0.0001</b>		<b>0.0013</b>	
HR (95% CI)	<b>Nivolumab vs ipilimumab 0.66 (0.54, 0.81)</b>		<b>Placebo vs ipilimumab 1.33 (1.11, 1.56)<sup>a</sup></b>	
	<b>Indirect comparison: nivolumab vs placebo</b>			
<b>Indirect HR (95% CI)</b>	<b>0.50 (0.38, 0.65)<sup>b</sup></b>			

AJCC = American Joint Committee on Cancer; CI = confidence interval; HR = hazard ratio; NC = not calculable; RFS = recurrence-free survival

<sup>a</sup> HR for placebo versus ipilimumab.

<sup>b</sup> Indirect HR for RFS, based on the 18 months follow-up was identical

Figures in bold are statistically significant.

Source: Table 47, p145 of the resubmission

6.16 The indirect HR for RFS, based on the 24 months follow-up data, was the same as that obtained with 18 months follow-up. The indirect HR was statistically significant favouring nivolumab over placebo (HR = 0.50; 95% CI: 0.38, 0.65).

6.17 The ESC noted in CA238 the distribution of individual RFS events was similar across the treatment groups (local recurrence was 18% of RFS events for nivolumab versus 21% for ipilimumab; regional recurrence 20% versus 17%; distance recurrence 57% versus 59%; death 0% versus 2%; disease at baseline 0.6% versus 0.9%; new primary melanoma 4% versus 2%; Study CA238 interim CSR, Table S.5.3). Corresponding data were not presented in the resubmission and could not be identified from the CA029 CSR.

6.18 Table 6 summarises the indirect comparison results for the secondary outcome of distant metastases free survival (DMFS).

**Table 6: Indirect comparison of DMFS between nivolumab (minimum of 24 months follow-up) and placebo (median follow-up of 5.3 years) via common reference ipilimumab**

Trial ID	Population	Intervention	Common reference	Main comparator	Direct HR <sub>DMFS</sub> (95% CI) <sup>a</sup>	Indirect HR <sub>DMFS</sub> (95% CI) NIVO vs. PBO Result < 1 favours NIVO
CA238	All patients: Stage IIIB, IIIC or IV	NIVO	IPI	-	0.76 (0.59, 0.98)	0.58 (0.42, 0.79)
CA029	ITT: Stage IIIA, IIIB, IIIC	-	IPI	PBO	1.32 (1.09, 1.56)	

CI = confidence interval; DMFS = distant metastasis-free survival; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; PBO = placebo

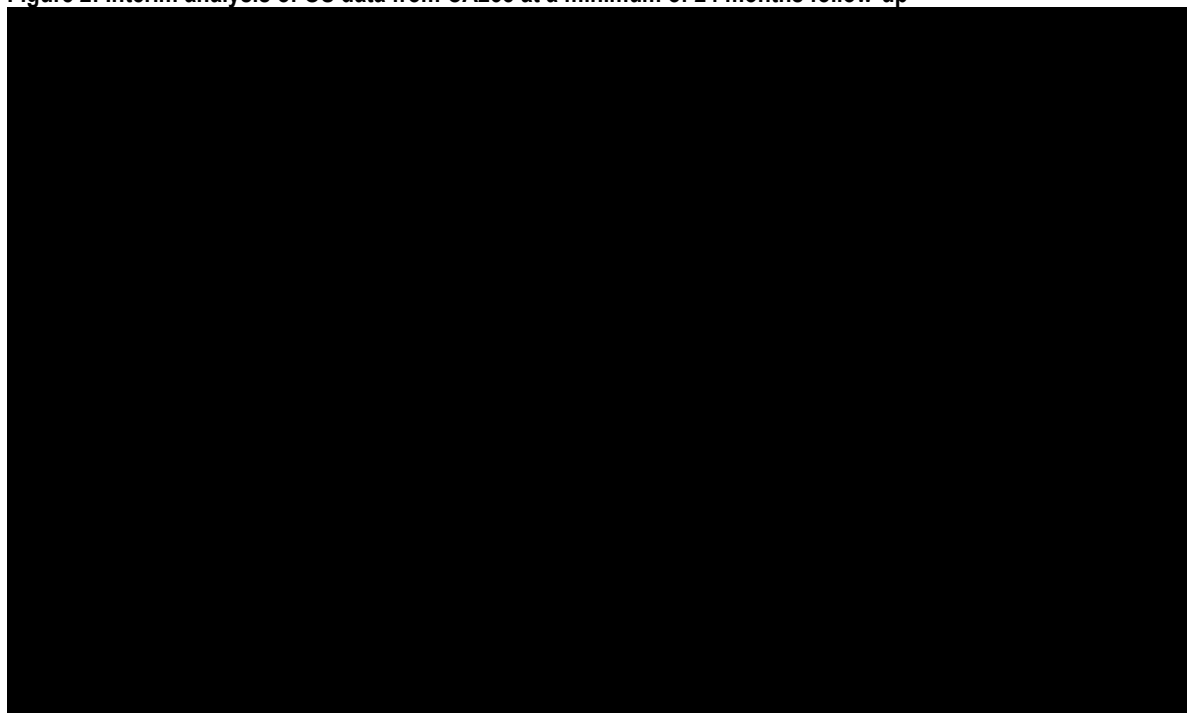
Source: Table 50, p149 of the resubmission

<sup>a</sup> For Trial CA184029 the results were presented as PBO vs. IPI i.e., the reciprocal of the result for IPI vs. PBO reported in the CSR (HR<sub>DMFS</sub> IPI vs. PBO = 0.76)

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- 6.19 The indirect HR for DMFS was statistically significant in favour of nivolumab ( $HR_{DMFS} = 0.58$ , 95% CI: 0.42, 0.79). These results were similar to those using 18 months follow up data ( $HR_{DMFS} = 0.55$ , 95% CI: 0.40, 0.77).
- 6.20 The ESC noted in CA238 nearly all DMFS events were distant metastases (92% of DMFS events for both the nivolumab and ipilimumab treatment arms; death 7% versus 6%; disease at baseline 0.9% versus 1.6%; CA238 interim CSR Table S.5.15). Similarly in CA029 nearly all DMFS events were distant metastases (87% of DMFS events for both ipilimumab and placebo; death 13% for both ipilimumab and placebo).
- 6.21 The pre-PBAC response provided a descriptive analysis of OS at the 24 month data lock of CA238 – see Figure below. At 24 months, [REDACTED] deaths had occurred; approximately [REDACTED]% of the protocol-expected number. Of the [REDACTED] deaths, [REDACTED] were in the ipilimumab arm and [REDACTED] were in the nivolumab arm.

**Figure 2: Interim analysis of OS data from CA238 at a minimum of 24 months follow-up**



OS = overall survival

Source: Figure 1, p1 of the pre-PBAC response

- 6.22 There were no updated quality of life (QoL) data. A formal indirect comparison of QoL data was not presented in the previous submission. This was conducted for the resubmission, which showed that there were no significant differences between nivolumab and placebo, in time to deterioration from baseline on QoL scores, except for dyspnoea which favoured placebo.
- 6.23 The resubmission presented indirect comparisons between nivolumab (minimum 24 months follow up) and near market comparators, pembrolizumab and DAB+TRAM, using placebo as the common reference. As the comparative RFS estimate used for

nivolumab versus placebo was indirect and synthesised using the CA238 and CA029 trials, these near market comparisons were 2-step indirect comparisons and were thus associated with a high level of uncertainty.

- 6.24 The DAB+TRAM COMBI-AD trial specifically included patients with tumours which were BRAF mutation positive only. No data for nivolumab in BRAF mutation positive patients were used for the indirect comparisons. For RFS, there was no statistically significant difference between nivolumab and pembrolizumab (HR = 0.88; 95% CI: 0.60, 1.28) or between nivolumab and DAB+TRAM (HR = 1.06; 95% CI: 0.77, 1.48).

### Comparative harms

- 6.25 There were no new safety data from the previous submission. The ESC advised that adjuvant therapy did not appear to present any new signals or safety concerns.

### Benefits/harms

- 6.26 A summary of the comparative benefits for nivolumab versus placebo is presented in Table 7. As was noted in the previous consideration of nivolumab (paragraph 6.24, Nivolumab PSD, July 2018), the higher exposure to ipilimumab and the longer duration of follow-up in CA029 compared to CA238 impeded the quantification of relative harms associated with nivolumab compared with placebo.

Table 7: Summary of comparative benefits for nivolumab versus placebo

Benefits				
Time-to-event outcome RFS				
	Nivolumab	Ipilimumab	Placebo	HR (95% CI)
<b>CA238: Stage IIIB, IIIC or IV, 7<sup>th</sup> AJCC edition</b>				
Events <sup>1</sup> , n/N (%)	171/453 (37.7%)	221/453 (48.8%)	-	0.66 (0.54, 0.81)
Median RFS, months (95% CI)	30.75 (30.75, NC)	24.08 (16.56, NC)	-	-
<b>CA029: Stage IIIA, IIIB, or IIIC, 6<sup>th</sup> AJCC edition</b>				
Events <sup>2</sup> , n/N (%)	-	234/475 (49.3%)	294/476 (61.8%)	1.33 (1.11, 1.56)
Median RFS, months (95% CI)	-	26.1 (19.3, 39.3)	17.1 (13.4, 21.6)	-
<b>Indirect comparison (nivolumab versus placebo)</b>				<b>0.50 (0.38, 0.65)</b>

<sup>1</sup> Updated 6 months RFS data from the previous submission: Minimum follow-up 2 years, December 2017 database lock

<sup>2</sup> Unchanged from the previous submission: Median follow-up 2.7 years

AJCC = American Joint Committee on Cancer; CI = confidence interval; HR = hazard ratio; NC = not calculable; RFS = recurrence-free survival

Source: Table 47, p145 of the resubmission.

- 6.27 On the basis of the indirect comparison presented in the resubmission, there was a 50% reduction in the risk of recurrence associated with nivolumab over a minimum duration of follow-up of 2 years, compared with placebo over a median duration of follow-up of 2.7 years. Interpretation of the magnitude of this indirect estimate should consider the high uncertainty concerning the magnitude of the effect due to the heterogeneity across the trials, the diminished applicability of the results to the proposed target population in clinical practice, and the insufficiency of RFS to capture the survival benefit from the overall treatment of these patients. The impact of adjuvant nivolumab therapy on subsequent outcomes relating to the use of nivolumab therapy for patients with unresectable or metastatic disease also remains unclear. The

ESC agreed with this interpretation. The ESC also noted on the basis of the indirect comparison there was a 42% reduction in the risk of a distant relapse and that the impact of distant relapse on subsequent costs and outcomes is greater than for locoregional relapse.

***Clinical claim***

- 6.28 As an adjuvant therapy for completely resected Stage III and IV melanoma, the resubmission described nivolumab as superior in terms of effectiveness and “moderately” inferior in terms of safety, compared to placebo.
- 6.29 The evaluation considered that, due to the concerns regarding the indirect nature of the comparison and related transitivity issues between the trials, the magnitude of the treatment effect was highly uncertain, particularly across the different disease sub-stages.
- 6.30 The limited OS data provided from the nivolumab CA238 trial was very immature and did not provide direct clinical evidence that the observed improvement in RFS would translate to an improvement in OS.
- 6.31 The magnitude of the RFS benefit associated with nivolumab versus placebo could not be determined for Stage IV disease as the comparator trial, CA029, did not enrol patients with this disease stage.
- 6.32 There was insufficient evidence to determine the incremental effectiveness of nivolumab in patients with Stage IIIA melanoma, as these patients were underrepresented in CA238. The PBAC considered that the benefit to risk ratio was uncertain in these patients, but it was likely to be modest.
- 6.33 The PBAC considered that the claim that nivolumab was superior to placebo in terms of comparative effectiveness was reasonable in patients with Stage IIIB, IIIC and IIID and Stage IV completely resected melanoma; however, considered that, due to the indirect nature of the comparison and the immaturity of the data, the magnitude of the treatment effect was highly uncertain.
- 6.34 The PBAC again considered that the claim that nivolumab was inferior compared to placebo in terms of comparative safety was reasonable.

***Economic analysis***

- 6.35 The resubmission presented a stepped economic evaluation based on an indirect comparison of randomised trials. The type of economic evaluation presented was a cost-utility analysis.
- 6.36 Table 8 below contains a summary of the key components of the economic evaluation.

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**Table 8: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost utility analysis
Outcomes	Life-years; quality-adjusted life years
Time horizon	30 years in the model base case (i.e. lifetime). This remains unchanged from the original submission. The evaluation noted that differences in overall survival (a key driver of the model) are not based on trial evidence relating to adjuvant nivolumab with a current standard of care, and are subject to substantial uncertainty, which is compounded by the long time horizon.
Method used to generate results	Partitioned survival model (i.e. area under the curve). This remains unchanged from the original submission.
Health states	Recurrent free disease; locoregional disease; distant metastatic disease; death
Cycle length	The area under the curve was assessed at 3 monthly intervals. This remains unchanged from the original submission.
Allocation to health states	Health state allocation over time was determined using RFS, DMFS and OS curves in line with partitioned survival model design. OS curves for the observation arm are based on Australian natural history data (Haydu, 2017) together with adjustments to reflect efficacy of modern treatments in the metastatic setting. RFS and DMFS curves for the observation arm of the model are based on the CA029 trial. All curves are extrapolated out using parametric survival curves. RFS, DMFS and OS curves for the nivolumab arm were constructed by application of hazard ratios to the observation survival curves.
Discounting	5% for outcomes and costs
Software	Excel 2016

DMFS = distant metastatic free survival; OS = overall survival; RFS = recurrent free survival

Source: Table 58, Section 3 of the resubmission

- 6.37 The economic model was updated from the previous submission (see Table 2).
- 6.38 The structure of the economic model was altered from a three-health state model (recurrent-free disease, recurrent disease and dead) to a four health state model (recurrent-free disease, locoregional recurrence, distant metastatic disease and dead), based on the PBAC's previous concern that a single recurrent-disease health state (in combination with static health state costs and utilities) was unlikely to reflect the outcome of patients treated in the adjuvant setting over the time horizon of the model (paragraph 7.6, Nivolumab PSD, July 2018). This ESC considered that the change in model structure was appropriate.
- 6.39 The ESC advised that the extent of extrapolation required with the use of a partitioned survival model rendered the results of the economic analysis highly uncertain. In addition, interpretation of the model results was hindered because recurrence events were not tracked separately, including the treatment and outcomes for each of these events. A Markov model would allow for the use of both observed data and external evidence to estimate the implications of a recurrence event, as traditionally used to evaluate therapies in the adjuvant setting. Substantial uncertainty in the cost-effectiveness ratios would remain due to immature OS data, but a Markov model would facilitate more detailed investigation of the effects of specific components of the pathway, e.g. transitions from local to metastatic recurrence, from and metastatic

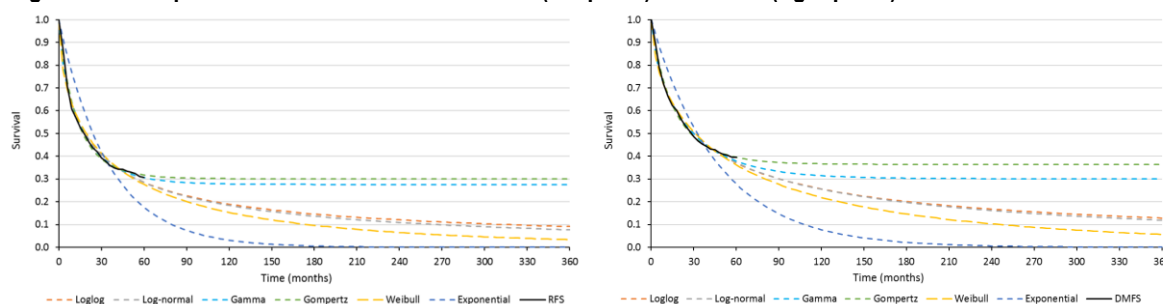
recurrence to death, and background mortality in the recurrence-free and local recurrence states.

6.40 Consistent with the original submission, the resubmission used the Kaplan Meier (KM) curves from the placebo arm of CA029 to construct the RFS and DMFS curves for the observation arm for the first five years. These curves were extrapolated out to 30 years using the log-normal parametric function; however, the evaluation noted that:

- there were a number of concerns regarding the applicability of CA029 to the proposed PBS population, particularly in terms of disease staging; and
- the log-normal extrapolations for the RFS and DMFS curves were not reasonable. Beyond year 15, the per-cycle hazard of dying from all-cause mortality (which is only captured in the OS curve) was greater than the per-cycle hazard of recurrence or death (represented by the RFS curve). This implied that those patients who were recurrence-free during this time had a better survival than the general population, which is implausible.

6.41 The ESC agreed that the log-normal extrapolations may not be reasonable. The ESC further noted the large variation in the estimated RFS and DMFS depending on the function used (Figure 3). The ESC advised that a function which predicts a reduced risk of recurrence over time may be clinically appropriate, although noted the gamma and Gompertz models were extreme with very few events in the extrapolated period.

Figure 3: Fitted parametric survival curves for RFS (left panel) and DMFS (right panel)



Source: figures 42 and 43, p189 of the resubmission

6.42 The modelled treatment effects of nivolumab, in terms of RFS and DMFS, were based on the application of the HRs from the indirect comparison (0.50 and 0.58 respectively, as described above) for the first three years of the model. Beyond Year 3, a HR of 1 was assumed for both curves, with neither converging during the 30 year time horizon. The ESC advised that convergence of the curves would be appropriate as there is currently insufficient data to determine if nivolumab delays or prevents recurrence (see Figure 5 for a comparison of the curves for RFS, DMFS and OS in the base case and with 20 year convergence). The PBAC, noting the immature and limited OS trial data, considered that convergence of the curves over 15 years would be more reasonable.

6.43 OS for the observation arm was constructed from a combination of melanoma specific survival (MSS) from Haydu (2017) and background population survival from Australian life tables (ABS 2017) for the first 15 years. MSS was extrapolated from Year 15 to Year 30 based on the Year 10 to 15 MSS data from Haydu (2017) and applying the log-normal parametric function. Haydu (2017) presented the conditional MSS estimates developed from a cohort of 4,540 patients diagnosed with Stage III melanoma treated at a single Australian institution between 1970 and 2013. The evaluation considered that the patient population in Haydu (2017) was unlikely to be applicable to the proposed PBS population as:

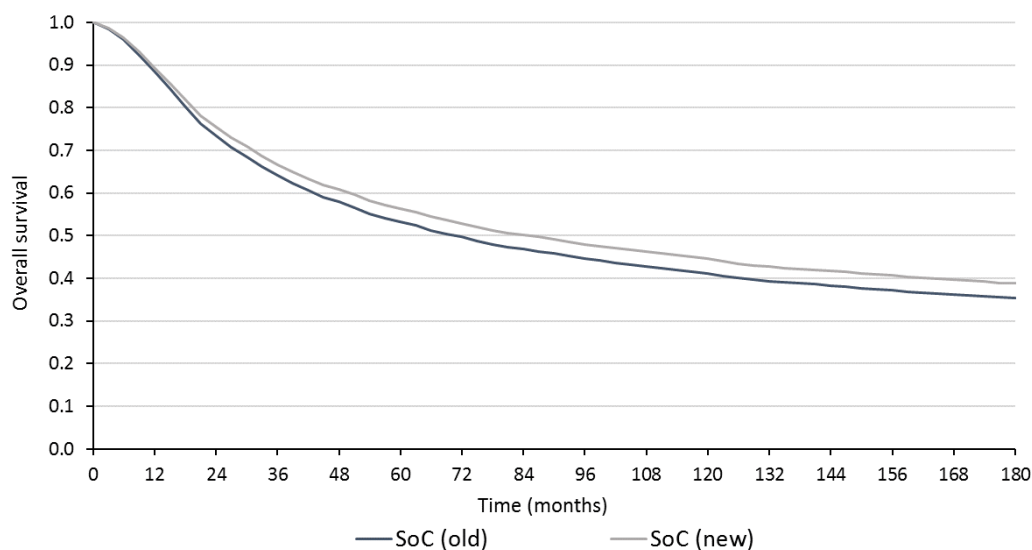
- it included patients with both resected and unresected Stage III disease;
- it only included patients with Stage III disease. The requested listing is for patients with completely resected Stage III or Stage IV disease;
- the distribution of patients by sub-stage may not reflect the distribution of patients likely to receive adjuvant treatment;
- it included patients diagnosed between 1970 and 2013. Therefore, overall survival estimates from this data source are unlikely to reflect the efficacy of modern surgical interventions and subsequent systemic therapy. The resubmission attempted to adjust the survival curve by applying the modelled average survival gain associated with ipilimumab (1.47 years) over 30 years from the November 2012 ipilimumab PBAC submission. However, this did not reflect the efficacy of newer systemic therapies such as PD-1 inhibitors in the unresectable or metastatic melanoma setting; and
- it was noted that the proportion of patients classified using the AJCC 8<sup>th</sup> edition staging system in Haydu (2017) differed from that observed in the nivolumab PAP dataset. Patients seeking treatment on the nivolumab PAP (N = 241) included a greater proportion of patients with Stage IIIA (10% vs 4.8%), and Stage IV (14% vs 0%) disease.

6.44 A comparison of the unadjusted OS curve ('SoC (old)'; based on MSS from Haydu (2017) and the Australian life tables), and the OS curve adjusted for modern unresectable or metastatic treatments ('SoC (new)' based on modelled average survival gain associated with ipilimumab (1.47 years) over 30 years), is provided in Figure 4 below. The ESC noted OS (SoC (new)) at 3 years was approximately 67%, which was low in comparison to that observed at 3 years in the observation arm of the COMBI-AD DAB+TRAM study (approximately 77%<sup>††</sup>), although it was noted that the COMBI-AD trial only included Stage III BRAF mutant melanoma patients. To better account for the current unresectable or metastatic treatment options, the pre-PBAC response proposed changing the OS HR adjustment from 0.91 (1.47 years additional survival gain) to 0.89 in the revised base case, providing SOC patients receiving unresectable or metastatic treatment with an additional 1.80 life years.

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<sup>††</sup> Long et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *NEJM*. 2017; 377(19):1813-1823.

Figure 4: OS curves applied in the model, ‘SoC (old)’ (based on Haydu 2017 and Australian life tables) and ‘SoC (new)’ (applied in the base case)



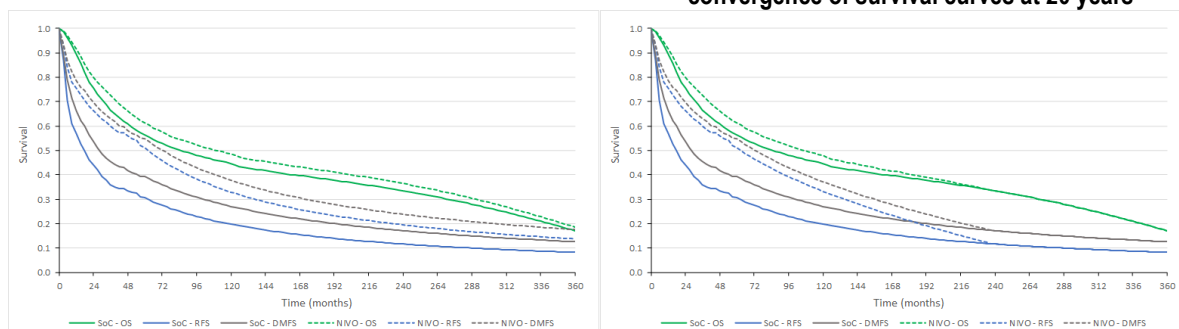
SoC = standard of care

Source: figure 40, Section 3 of the resubmission

- 6.45 Given the lack of OS data from CA238, the resubmission constructed an OS curve for nivolumab by applying the OS HR from CA029 for ipilimumab versus placebo (not adjusted to account for modern unresectable or metastatic treatments) for years 1 to 3. Beyond this, the model assumed a HR of 1, so the nivolumab and placebo curves did not converge over the 30 year time horizon. The resubmission stated that use of this HR was conservative and assumed that nivolumab was non-inferior to ipilimumab in terms of OS. The evaluation considered that it would be reasonable to expect that a change in OS due to adjuvant treatment would be influenced by both changes in the recurrence rate and the effectiveness of subsequent therapies in an unresectable or metastatic setting. Therefore, the HR from CA029 reflected the use of adjuvant ipilimumab followed by an older standard of care. It was unclear whether the same HR would be observed in a comparison of adjuvant melanoma followed by modern unresectable or metastatic treatments (including PD-1 inhibitors) to observation followed by other modern unresectable or metastatic treatments. The structure of the economic model did not allow isolation of the impact of the availability of adjuvant treatment of melanoma on recurrence or the improvement in efficacy of treatments in the unresectable or metastatic setting.
- 6.46 The RFS, DMFS and OS curves by treatment group over the time horizon of the model, and with a sensitivity analysis assuming convergence at 20 years, are presented in the figures below. As noted, the ESC considered that convergence may be appropriate given the lack of OS data and the uncertainty regarding delay versus prevention of recurrence. The pre-PBAC response considered that convergence of the overall survival curves at 15 or 20 years was implausible based on the available trial data, as when convergence from 5 to 15 years was applied, this implied HR for OS = 1.20; RFS

= 1.69; and DMFS = 1.53. The pre-PBAC response suggested that convergence from 5 to 30 years resulted in more realised model outputs and HRs for OS = 1.07; RFS = 1.39; and DMFS = 1.29. This approach was incorporated into a revised base case presented in the pre-PBAC response. The PBAC, noting the immature and limited OS trial data, considered that convergence of the curves over 15 years would be more reasonable.

**Figure 5: Comparison of modelled survival curves, base case (left panel) and sensitivity analysis (right panel)**  
**3 years of treatment effect followed by equivalent probabilities of recurrence and death to 30 years** (left panel)  
**3 years of treatment effect followed by equivalent probabilities of recurrence and death to 5 years, and convergence of survival curves at 20 years** (right panel)



Source: figures 49 and 50, pp197-8 of the resubmission.

DMFS = distant metastatic free survival; NIVO = nivolumab; OS = overall survival; RFS = recurrent free survival; SoC = standard of care.

- 6.47 The health state utilities associated with recurrent disease have changed due to the altered model structure. In the original submission, the utility associated with recurrent disease was 0.737, sourced from Middleton (2017). In the current submission, utilities associated with the recurrent disease health states were 0.737 for the locoregional recurrent disease health state and 0.62 for the distant metastatic disease health state, which were also sourced from Middleton (2017).
- 6.48 The ESC noted the vignette-based utility applied for recurrence free disease was 0.855. For local recurrence, the utility was 0.737 and this was applied for the entire model duration. The ESC considered that over time, the utility for local recurrence would rebound to be the same as for the recurrence free state. For distant recurrence the utility was 0.62, which the ESC noted reflected a post progression health state. Overall, the ESC considered the utility values favoured nivolumab, and that values of 0.855 for local recurrence and 0.737 for distant recurrence may be more appropriate. The pre-PBAC response stated that the ESC utility values did not incorporate post-progression survival. The pre-PBAC response applied revised base-case utility values midway between those proposed in the resubmission and ESC, i.e. for local recurrence the utility was 0.796 and for distant recurrence is was 0.679. The PBAC considered that these values were reasonable.
- 6.49 The key drivers of the model are summarised in the table below.

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

Description	Method/Value	Impact
OS in the observation arm	Constructed from a combination of MSS from Haydu (2017) and background population survival from Australian life tables (ABS 2017). OS curve was adjusted upward to provide an additional 1.47 life years (undiscounted), consistent with the economic model of ipilimumab versus placebo, from the November 2012 submission. These OS estimates were not applicable to the proposed patient population (see paragraph 6.43) and were likely to impact the results of the model.	Unclear, although may favour nivolumab.
Treatment benefit of nivolumab in terms of OS	HR assumed to be the same as ipilimumab versus placebo in CA029. This was inappropriate as it did not reflect the efficacy of a modern standard of care upon recurrence, nor changes in OS due to improvements in RFS. The direction of bias was unclear.	Unclear
Duration of treatment benefit	Differences in survival (RFS/DMFS/OS) assumed to continue until the end of the time horizon (30 years).	High, favours nivolumab
Utility values for the distant metastatic disease health state	Lower utility value used for the distant metastatic disease health state (0.62), and longer time (per recurrence) spent in this health state in the observation arm compared to nivolumab arm. The ESC considered the utility value for local recurrence should rebound towards that for RFS.	Moderate, favours nivolumab

ABS = Australian Bureau of Statistics; DMFS = distant metastatic-free survival; ESC = Economic Sub-Committee; HR = hazard ratio; IPI = ipilimumab; MSS = melanoma specific survival; OS = overall survival; RFS = recurrence-free survival  
Source: Compiled during the evaluation

6.50 The pre-PBAC response provided a revised economic model, which addressed the ESCs concerns regarding convergence, utility values and the availability of newer effective treatments in the unresectable or metastatic setting by adopting the inputs in the following table.

**Table 10: Revised economic model inputs**

Assumption	Resubmission	ESC advice	Revised base case
Convergence	Not applied	Start 5 years; end 15 years	Start 5 years; end 30 years
Utility values	LR = 0.737; DR = 0.620	LR = 0.855; DR = 0.737	LR = 0.796; DR = 0.679
SoC adjustment factor	0.91	0.91	0.89
Proposed price per 100 mg vial	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

DR = distant recurrence; ESC = Economic Sub-Committee; LR = local recurrence; SoC = standard of care  
Source: Table 1, p2 of the pre-PBAC response

6.51 Results of the stepped economic evaluation, and the revised base case presented in the pre-PBAC response, are provided in the table below.

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Table 11: Results of the stepped economic evaluation

Step	Incremental cost	Incremental outcome	ICER
<b>Step 1: “Trial based”</b> <ul style="list-style-type: none"> <li>Incremental cost per recurrence-free survival year</li> <li>RFS curves for the observation arm from the PBO arm of CA029</li> <li>NIVO RFS curve derived using the indirect HR of NIVO to observation via IPI for RFS</li> <li>Include drug acquisition costs only</li> <li>3-year trial duration</li> </ul>	██████████	0.5201	██████████
<b>Step 2: Inclusion of OS</b> <ul style="list-style-type: none"> <li>Incremental cost per life year gained</li> <li>OS curves for observation arm from the PBO arm of CA029</li> <li>NIVO OS curve derived using an indirect HR of NIVO to observation via IPI where the NIVO to IPI HR is assumed to be 1.00</li> </ul>	██████████	0.1270	██████████
<b>Step 3: Transformation of health states to utility values and inclusion of all non-adjuvant treatment related costs</b> <ul style="list-style-type: none"> <li>Incremental cost per QALY gained</li> <li>DMFS curves for observation arm from the PBO arm of the CA029 trial</li> <li>NIVO DMFS curve derived using the indirect HR of NIVO to observation via IPI for DMFS</li> <li>Include health state costs and utility values</li> <li>Include costs of metastatic treatment</li> </ul>	██████████	0.1616	██████████
<b>Step 4: Extrapolation of model duration</b> <ul style="list-style-type: none"> <li>Incremental cost per QALY gained</li> <li>Extrapolation of observation curves using parametric survival functions</li> <li>30 years' duration</li> </ul>	██████████	0.8716	██████████
<b>Step 5: PBS population adjustments</b> <ul style="list-style-type: none"> <li>Incremental cost per QALY gained</li> <li>OS curves for the observation arm of the model from Haydu (2017)</li> </ul>	██████████	0.9339	██████████
<b>Step 6: PBS circumstances of use adjustments</b> <ul style="list-style-type: none"> <li>Incremental cost per QALY gained</li> <li>HR applied to observation OS curve to increase survival to account for effective modern metastatic treatments</li> </ul>	██████████	0.7923	██████████
<b>Pre-PBAC response revised base case</b> <ul style="list-style-type: none"> <li>Convergence from 5 to 30 years (base case: no convergence)</li> <li>Utility values updated RFS = 0.855 (unchanged); LR = 0.796 (base case: 0.737); and DR = 0.6785 (base case: 0.62)</li> <li>SoC adjustment factor = 0.89 (base case: 0.91)</li> <li>Price = \$955/100 mg vial (base case: \$1,200)</li> </ul>	██████████	0.6328	██████████

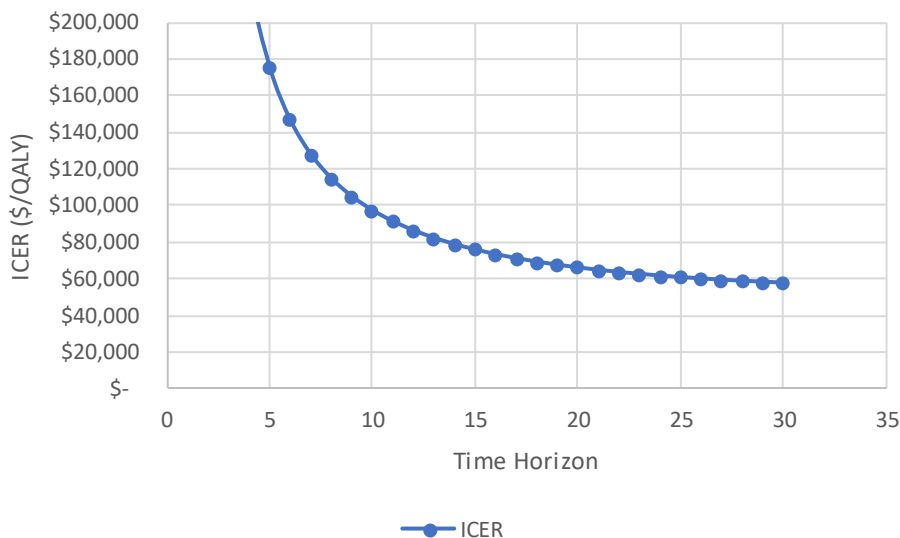
DMFS = distant metastatic-free survival; DR = distant recurrence; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IPI = ipilimumab; LR = local recurrence; NIVO = nivolumab; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo; QALY = quality-adjusted life-year; RFS = recurrence-free survival; SoC = standard of care

Source: Compiled during the evaluation based on information presented in Table 88, Section 3 and Section 3.1.6 of the resubmission and Table 2, p2 of the pre-PBAC response.

The redacted table shows ICERs in the range of \$45,000/QALY – more than \$200,000/QALY.

6.52 Figure 6 provides a summary of the relationship between the ICER and the time horizon of the model. The results are sensitive to the time horizon of the model.

**Figure 6: Relationship between the time horizon and resulting ICER for the submission base case**



ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Source: Compiled during the evaluation based on information presented in 'AdjvNIVO\_Section3Model.xlsx'

6.53 The results of selected sensitivity analyses are provided in Table 12. Given its concerns about the transitivity of the trials used in the ITC, the lack of convergence of the survival curves, and the appropriateness of the utility values for local and distant recurrence, the ESC suggested that the PBAC may find additional sensitivity analyses informative, and these have been included below. In addition to the parameters noted by ESC, the PBAC noted the ICER was sensitive to the distant metastatic disease recurrence non drug cost, with the ICER ranging from \$45,000 - \$75,000/QALY to \$45,000 - \$75,000/QALY when these costs were varied by ±50%.

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Table 12: Results of selected sensitivity analyses

Variable tested (base case)	Sensitivity analysis	Incremental costs	Incremental QALYs	ICER
Base Case	-		0.7923	
<b>Extrapolation variables</b>				
Parametric survival method (Log-normal) <sup>b</sup>	Gamma		0.8493	
	Weibull		0.7459	
	Exponential		0.6076	
Convergence extrapolation (HR based assumptions until start variable in years, then linear decline in incremental effect until converge end variable in years), for RFS, DMFS and OS curves	Start 5, End 10		0.3935	
	Start 5, End 15		0.5111	
	Start 5, End 20		0.6117	
	Start 5, End 30		0.7726	
<b>Treatment effects<sup>a</sup></b>				
NIVO vs SoC HR <sub>RFS</sub> (0.50)	95% LCL 0.38		0.8952	
	95% UCL 0.65		0.7025	
NIVO vs SoC HR <sub>DMFS</sub> (0.58)	95% LCL 0.42		0.8848	
	95% UCL 0.79		0.7216	
IPI vs SoC HR <sub>OS</sub> (0.72)	95% LCL 0.58		1.0748	
	95% UCL 0.88		0.4893	
Survival benefit of modern metastatic therapies: SoC(New) vs SoC(Old) HR <sub>OS</sub> (0.91)	1.00 (no survival benefit for modern metastatic treatments)		0.9339	
	0.85 (≈30 months survival benefit <sup>a</sup> )		0.6885	
<b>Utility values</b>				
LD recurrence utility value (0.737)	Both 0.62		0.8498	
	Both 0.6785 (average)		0.7558	
DMD recurrence utility value (0.620)	Both 0.737		0.6617	
	Both 0.8 (NIVO and IPI metastatic clinical trials, Tilden 2017)		0.5605	
<b>Costs</b>				
DMD recurrence health state non-drug costs (\$11,429 per annum)	Decreased 50%		0.7923	
	Increased 50%		0.7923	
Recurrent treatment costs (\$66,502 per patient)	Decreased 50%		0.7923	
	Increased 50%		0.7923	
<b>Additional analysis requested by the ESC</b>				
NIVO vs SOC: HR <sub>RFS</sub> (0.50) and HR <sub>DMFS</sub> (0.58)	NIVO vs SOC: HR <sub>RFS</sub> 95% UCL 0.65; HR <sub>DMFS</sub> 95% UCL 0.79		0.5958	
LD recurrence utility value (0.737) DMD recurrence utility value (0.620)	LD utility (0.855) DMD utility (0.737)		0.6037	
Utilities: LD utility (0.737) DMD utility (0.620) Convergence: Not applied	Utilities: LD utility (0.855) DMD utility (0.737) Convergence: Start 5, End 10.		0.2787	
Utilities: LD utility (0.737) DMD utility (0.620)	Utilities: LD utility (0.855) DMD utility (0.737)		0.3670	

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Variable tested (base case)	Sensitivity analysis	Incremental costs	Incremental QALYs	ICER
Convergence: Not applied	Convergence: Start 5, End 15.			
Utilities: LD utility (0.737) DMD utility (0.620) Convergence: Not applied NIVO vs SOC: HR <sub>RFS</sub> (0.50) and HR <sub>DMFS</sub> (0.58)	Utilities: LD utility (0.855) DMD utility (0.737) Convergence: Start 5, End 15. NIVO vs SOC: HR <sub>RFS</sub> 95% UCL 0.65 HR <sub>DMFS</sub> 95% UCL 0.79	████████	0.2952	████████

DMD = distant metastatic disease; DMFS = distant metastases free survival; ESC = Economic Sub-Committee; HR = hazard ratio; IPI = ipilimumab; LD = locoregional disease; NIVO = nivolumab; OS = overall survival; QALY = quality-adjusted life year; RFS = recurrence free survival; SoC = standard of care; UCL = upper confidence limit;

<sup>a</sup> Due to the use of a partitioned survival model structure, changes in the effectiveness of nivolumab in terms of RFS and DMFS does not impact overall survival.

<sup>b</sup> The extrapolation of DMFS and RFS curves using some of the parametric functions produced unexpected results. For example, using the gamma parametric function to extrapolate both the RFS and DMFS resulted in a much lower risk of recurrence in the extrapolated portion of the model, which, all else being equal, would be expected to increase the ICER. However, the ICER in this sensitivity analyses decreased. This is likely due to assumptions made in the implementation of the partitioned survival model: 1) The per-cycle hazard of patients transitioning from the RFS or LD health states (as evidenced by the flat RFS/DMFS survival curves) was lower than the per-cycle hazard of patients dying (either from melanoma-related causes or from all-cause mortality), which meant that patients were preferentially moved from the DMFS, then LD disease states as they die; and 2) The OS curve crossed the RFS and DMFS curves much sooner in the nivolumab arm which resulted in a larger proportion of patients remaining in the RF health state compared to the base, despite the overall survival remaining the same.

Source: Tables 93, 94, 95, 96 and 97, Section 3 of the resubmission

The redacted table shows ICERs in the range of \$45,000/QALY – more than \$200,000/QALY.

**Drug cost/patient/course: \$ ██████████**

6.54 This cost was based on a recommended dose of 3 mg/kg administered every two weeks and a mean (SD) weight of 81.33 (SD: 19.42) kilograms per person (from CA238), assuming a normal distribution around the mean. The expected number of whole 20 mg dispensing intervals (i.e. incorporating wastage, as nivolumab may be dispensed in 20 mg intervals for doses over 80 mg) per dose was calculated to be 12.70, which equated to a mean dose 254 mg per person. This was multiplied by the expected average number of doses of nivolumab (19.6 doses) as observed in CA238 (i.e. 39.2 weeks' total duration) and assuming 70% will be dispensed for use in a

private hospital (based on PBS statistics for ipilimumab, nivolumab and pembrolizumab).

- 6.55 For a maximum 12-month course of treatment (i.e. 26 administrations), with 3 mg/kg every two week dosing:
- Drug cost/patient/course: \$ [REDACTED]
  - Administration cost/patient/course: \$ [REDACTED]
- 6.56 With fixed dose 480 mg every four week dosing:
- Drug cost/patient/course: \$ [REDACTED] (13 administrations for maximum 12 month course of treatment) or \$ [REDACTED] (9.8 doses, same treatment duration as CA238)
  - Administration cost/patient/course: \$ [REDACTED] (13 administrations) or \$ [REDACTED] (9.8 administrations).
- 6.57 This compared to a drug cost/patient/course of \$ [REDACTED] in the previous submission. The assumption of 19.6 doses was consistent with the original submission; however the cost per 100 mg vial has changed from \$ [REDACTED] in the original submission to \$ [REDACTED] in the resubmission.

### **Estimated PBS usage & financial implications**

- 6.58 This submission was not considered by DUSC.
- 6.59 The submission used an epidemiological approach to estimate the likely extent of use of adjuvant nivolumab and the associated financial implications to the PBS/RPBS. Most of the data sources used in the financial analysis were changed from the previous submission. The number of patients likely to receive nivolumab adjuvant therapy was mainly estimated using Australian studies<sup>§§</sup> and national databases<sup>\*\*\*</sup>. Retreatment with nivolumab in the same (adjuvant) setting was not taken into account in the base case financial analysis, although such use was proposed by the resubmission. The size of the patient population initially diagnosed with earlier stages of disease that progress to Stage III or IV melanoma was estimated on the basis of a study<sup>†††</sup> which analysed RFS data from the Melanoma Institute Australia on an inception cohort of patients first diagnosed with Stage I or II melanoma in 1985-2009. The disease staging system and melanoma treatments of the included patients were outdated. In addition, the rate reported in the study is the recurrence of all disease stages, not only Stages III and IV. Therefore, the number of patients developing recurrent Stage III or IV

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<sup>§§</sup> Adler NR, Wolfe R, Kelly JW, Haydon A, McArthur GA, McLean CA, et al. Tumour mutation status and sites of metastasis in patients with cutaneous melanoma. *Br J Cancer*. 2017;117(7):1026-35.

Turner RM, Bell KJ, Morton RL, Hayen A, Francken AB, Howard K, et al. Optimizing the frequency of follow-up visits for patients treated for localized primary cutaneous melanoma. *J Clin Oncol*. 2011;29(35):4641-6.

<sup>\*\*\*</sup> Australian Cancer Incidence and Mortality (ACIM) book: melanoma of the skin (AIHW 2017). Available from: <https://www.aihw.gov.au/reports/cancer/acim-books/contents/acim-books>

National Cancer Control Indicators (NCCI) website: <https://ncci.cancer australia.gov.au/diagnosis/distribution-cancer-stage/distribution-cancer-stage>

<sup>†††</sup> Turner RM, Bell KJ, Morton RL, Hayen A, Francken AB, Howard K, et al. Optimizing the frequency of follow-up visits for patients treated for localized primary cutaneous melanoma. *J Clin Oncol*. 2011;29(35):4641-6.

disease from earlier stages may differ in clinical practice from the resubmission's estimate.

6.60 The resubmission expected that the use of adjuvant nivolumab would result in a decrease in the number of patients who experience disease recurrence and require treatment for unresectable Stage III or IV melanoma. It was assumed that the flow-on impact to the treatment costs in the unresectable or metastatic setting would commence 12 months post listing of adjuvant nivolumab (i.e. no cost offsets in Year 1 of listing). In subsequent years, the decrease in the costs of melanoma therapies in the unresectable or metastatic setting was estimated by applying 58% (the resubmission's estimate of the proportion of Stage IV patients that could receive adjuvant treatment) and 11% (difference in 10-Year DMFS rate between the nivolumab and observation arm in the economic model) to the extrapolated Risk Sharing Arrangement (RSA) caps (for PD-1 inhibitors and ipilimumab) or government expenditure (for BRAF/MEK inhibitors). The submission's approach raised a number of issues, including:

- PD-1 inhibitors, ipilimumab and BRAF/MEK inhibitors are currently listed on the PBS for treatment of unresectable Stage III or Stage IV melanoma. DMFS is not a reasonable proxy for estimating the avoidance of subsequent anti-cancer treatments, as patients with unresectable regional (Stage III) recurrent disease are also eligible for post-recurrence medicines;
- the resubmission assumed that the estimated 6.4%<sup>+++</sup> reduction in patients treated in the unresectable or metastatic setting would result in a 6.4% reduction in the RSA caps for PD-1 inhibitors and for ipilimumab. This implicitly assumed that the use of adjuvant nivolumab would not affect the distribution of post-recurrence treatments with PD-1 inhibitors, ipilimumab and BRAF/MEK inhibitors for unresectable or metastatic melanoma. This was unreasonable; and
- the expenditure cap for ipilimumab was not reached over the first 4 years of the Deed. The use of the ipilimumab RSA cap, not the actual government expenditure, to determine the reduction in PBS/RPBS cost for ipilimumab in the unresectable or metastatic setting due to the listing of adjuvant nivolumab, resulted in an overestimation of the associated cost offsets.

6.61 The extent of use and the financial implications to the government budget associated with the proposed listing of adjuvant nivolumab are summarised in the table below. Compared with the original submission, the net cost to the PBS/RPBS increased by approximately 50% in Year 1 of listing. This was due to the inclusion of grandfathered patients (N = 720; estimated on the basis of the current nivolumab PAP) and the removal of cost offsets in Year 1. In subsequent years, the PBS/RPBS cost of nivolumab did not change greatly from the previous submission as although the estimated number of patients likely to be treated increased by approximately 50% (primarily due

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<sup>+++</sup> 6.4% = 58% x 11%, where 58% is the proportion of Stage IV patients that could receive adjuvant treatment and 11% is DMFS prevented due to the use of adjuvant nivolumab

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to the inclusion of patients initially diagnosed with Stage I or II disease that experience recurrence with resectable Stage III or Stage IV disease), the resubmission proposed a lower price for nivolumab. In addition, the cost offsets were reduced by 24% to 40% compared to the original submission’s estimates.

- 6.62 The ESC noted that whilst the drug price for the 100 mg vial had been reduced by more than █%, the net implications to the PBS/RPBS were reduced by less than 4% compared to the previous submission. The ESC noted that this was driven by a significant increase in the forecast of treated patients compared to the July 2018 submission. In its consideration of the July 2018 submission, DUSC noted that the incident melanoma estimates that were used to quantify the eligible population were based on the diagnosis of primary disease and did not incorporate those patients diagnosed with earlier stages of disease that subsequently progress to later stages. The resubmission’s approach in incorporating patients with earlier stage disease progressing to Stage III or IV has introduced a large additional cohort of patients initiating nivolumab compared to the prior submission. The ESC also noted grandfathered patients accessing nivolumab in Year 1 of listing were included.

**Table 13: Comparison of the eligible populations derived for the July 2018 and March 2019 submissions**

	Year 1 (2019)	Year 2	Year 3	Year 4	Year 5	Year 6	Source/comments
<b>July 2018</b>							
Incident malignant melanoma	█	█	█	█	█	█	AIHW Cancer incidence projections (2012)
Patients eligible for nivolumab, Stage III or IV resectable	█	█	█	█	█	█	Stage III 8.68% and Stage IV 0.6% resectable, based on Balch (2001)
<b>March 2019</b>							
Incident malignant melanoma	█	█	█	█	█	█	ACIM books: melanoma of the skin (AIHW 2017).
Patients eligible, Stage III or IV at diagnosis	█	█	█	█	█	█	Stage III 3.0% and Stage IV 2.1% resectable, based on NCCI (2011)
Recurrent Stage I/II to Stage III/IV	█	█	█	█	█	█	Survival estimates from Turner (2011)
Completely resectable stage III	█	█	█	█	█	█	Proportion resectable was 86% for Stage III and 13% for Stage IV, based on a treatment survey
Completely resectable stage IV	█	█	█	█	█	█	
Grandfathered patients	█	█	█	█	█	█	Current nivolumab PAP, assumption
Total eligible patients for adjuvant therapy	█	█	█	█	█	█	Including grandfathered patients in Year 1

ACIM = Australia Cancer Incidence and Mortality; AIHW = Australian Institute of Health and Welfare; NCCI = National Cancer Control Indicators; PAP = patient access program

Sources: Table 102, p176 Section 4 of the July 2018 submission; Table 104, pp244-245 and Table 107, p247 of the March 2019 resubmission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

6.63 The PSCR suggested that the dosing regimen for adjuvant treatment should be aligned with the requested changes to other nivolumab listings, if recommended (i.e. allowing clinician choice between weight based dosing (3 mg/kg every two weeks) or fixed dosing (240 mg every two weeks or 480 mg every four weeks), item 6.14 refers). The PSCR suggested that the 480 mg every four weeks fixed dose regimen was the likely to be the most utilised regimen for adjuvant therapy. A sensitivity analysis was conducted for the 240 mg every two weeks dosing regimen in the resubmission, and is included in the table below.

6.64 The pre-PBAC response provided revised cost estimates which excluded Stage IIIA patients, adjusted grandfathered patients to better account of time on treatment and incorporated the revised proposed price.

**Table 14: Estimated use and financial implications**

	Year 1 (2019)	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	████	████	████	████	████	████
Number of scripts dispensed <sup>a</sup>	████	████	████	████	████	████
<b>Estimated financial implications of nivolumab in the adjuvant setting</b>						
Cost to PBS/RPBS	████████	████████	████████	████████	████████	████████
Copayments	████████	████████	████████	████████	████████	████████
Cost to PBS/RPBS less copayments Revised <sup>b</sup>	████████	████████	████████	████████	████████	████████
<b>Changed in costs for treatments in the unresectable or metastatic setting</b>						
PD-1 inhibitors	████████	████████	████████	████████	████████	████████
Ipilimumab	████████	████████	████████	████████	████████	████████
BRAF/MEK inhibitors	████████	████████	████████	████████	████████	████████
Total	████████	████████	████████	████████	████████	████████
<b>Net financial implications</b>						
Net cost to PBS/RPBS Revised <sup>b</sup>	████████	████████	████████	████████	████████	████████
Net cost to MBS	████████	████████	████████	████████	████████	████████
Net cost to PBS/RPBS/MBS Revised <sup>b</sup>	████████	████████	████████	████████	████████	████████
Sensitivity analysis: Fixed dose of 240 mg Q2W	████████	████████	████████	████████	████████	████████
<b>Estimates from the July 2018 submission (compiled during the evaluation)</b>						
<b>Estimated extent of use</b>						
Number of patients treated	████	████	████	████	████	████
<b>Estimated financial implications of nivolumab</b>						
Cost to PBS/RPBS less copayments	████████	████████	████████	████████	████████	████████
<b>Estimated financial implications for medicines to treat disease recurrence (avoided)</b>						
Cost to PBS/RPBS	████████	████████	████████	████████	████████	████████

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	Year 1 (2019)	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Net financial implications</b>						
Net cost to PBS/RPBS	██████████	██████████	██████████	██████████	██████████	██████████
Net cost to MBS <sup>c</sup>	██████████	██████████	██████████	██████████	██████████	██████████
Net cost to PBS/RPBS/MBS	██████████	██████████	██████████	██████████	██████████	██████████
<b>Pre-PBAC response revised estimates</b>						
Number of patients treated	████	████	████	████	████	████
Net cost to PBS/RPBS	██████████	██████████	██████████	██████████	██████████	██████████

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PD-1 = programmed cell death-1; Q2W = every 2 weeks; RPBS = Repatriation Pharmaceutical Benefits Scheme

<sup>a</sup> Assuming 19.6 scripts per patient as estimated by the submission.

<sup>b</sup> The resubmission incorrectly calculated the cost to the PBS/RPBS (excluding copayments) by the cost to the PBS/RPBS (including copayments) plus (not minus) copayments. This error was corrected during the evaluation.

<sup>c</sup> The submission assumed that the administration cost of nivolumab relates to MBS Item 13915. The expected number of drug administrations and MBS items per patient course is 19.6. The cost to the MBS per administration is \$55.30 (85% benefit).

Source: Table 107, p247, Table 110, p249, Table 114, p255, Table 115, p257 and Table 116, p258 of the resubmission and Table 106, Table 111, and Table 112 of the July 2018 submission and Table 3, p3 of the pre-PBAC response

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 more than \$100 million per year.

6.65 The main areas of uncertainty relating to the estimated financial implications of listing nivolumab in the adjuvant melanoma setting related to the:

- proportion of patients initially diagnosed with Stage I or II disease that experience a disease recurrence with resectable Stage III or Stage IV disease; and
- cost offsets in the unresectable or metastatic setting. The submission’s approach was not well justified in terms of the use of DMFS as a proxy for the avoidance of subsequent treatments for unresectable Stage III or Stage IV melanoma. The change of current RSA caps for treatments in the unresectable or metastatic setting due to the listing of adjuvant nivolumab was unknown. In addition, the use of the RSA cap in the financial analysis has overestimated the actual government expenditure for ipilimumab.

**Financial Management – Risk Sharing Arrangements**

6.66 The resubmission proposed a Special Pricing Arrangement (SPA). The resubmission did not provide any information on a potential Risk Sharing Arrangement (RSA) for nivolumab as adjuvant treatment for completely resected Stage III or IV melanoma.

6.67 A RSA, in the form of financial caps, applies to PD-1 inhibitors (i.e. nivolumab and pembrolizumab), to ipilimumab and to BRAF/MEK inhibitors. The availability of nivolumab at an earlier stage of treating melanoma will affect the extent of utilisation and, thus, the financial implications for all of the above medicines for unresectable Stage III or Stage IV melanoma.

- 6.68 The PBAC considered that the existing RSA should be extended to incorporate the proposed expansion of the nivolumab indication. To mitigate the uncertainty surrounding the extent of PD-1 inhibitors in both the adjuvant and unresectable or metastatic settings, the PBAC considered that a new deed should be negotiated that combines caps across the current PBS indication in unresectable or metastatic disease with the proposed adjuvant indication. The PBAC considered that the new deed should include hard caps with ■■■% rebates.

### ***Risk Management – Managed Access Program***

- 6.69 The resubmission proposed a Managed Access Program (MAP). The proposed MAP would see nivolumab initially listed on the PBS at the PBAC agreed ex-manufacturer price based on the current available evidence, including the assumption that the OS HR for nivolumab vs ipilimumab = 1.00, as applied in the base case of the economic model. Under the proposed conditions of the MAP, the ex-manufacturer price would then be subject to (and conditional upon a review of) a price adjustment based on the subsequent provision of final OS data from CA238.
- 6.70 The PBAC noted that the sponsor was willing to withdraw the proposed MAP as there was no certainty that there will be enough events to provide meaningful data at 48 months follow-up. The PBAC considered that any uncertainty was better mitigated through an RSA.

*For more details on PBAC's view, see Section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC decided not to recommend nivolumab as an adjuvant treatment for completely resected Stage III or IV melanoma. The PBAC again acknowledged that there was a high unmet clinical need for effective therapies to reduce the risks of recurrence of resected Stage III or IV melanoma, and considered that in some circumstances, recurrence was less likely for nivolumab compared to placebo. However, the PBAC remained concerned that there was uncertainty in the magnitude of the clinical benefit and in the incremental cost-effectiveness ratio due to the immaturity of the data, and that the estimated financial impact remained high and uncertain.
- 7.2 The PBAC acknowledged the consumer comments received for this item, noting that they described a range of benefits for adjuvant nivolumab including improved survival and quality of life.
- 7.3 In terms of the clinical place, the PBAC noted that the submission proposed that nivolumab would supplement routine care in completely resected Stage III and Stage IV melanoma patients, and that patients treated with nivolumab in the adjuvant setting would continue to be eligible to receive programmed cell death (PD-1) inhibitors or BRAF/MEK inhibitors in the unresectable or metastatic setting if they completed the 12 month adjuvant course without disease progression. The PBAC

noted that limited clinical evidence was presented to support retreatment. However, the PBAC considered that it would be clinically inappropriate to prevent retreatment if a patient had responded well to adjuvant therapy.

- 7.4 The PBAC noted that limited data were presented for patients with Stage IIIA disease in the CA238 trial and that patients with Stage IIIA disease have a relatively low risk of recurrence and a five year melanoma-specific survival rate of 93%. The PBAC therefore foreshadowed that PBS-subsidised treatment in the adjuvant setting should be restricted to patients with completely resected Stage IIIB, IIIC, IIID and Stage IV disease (staged using the 8<sup>th</sup> edition of the AJCC melanoma staging system).
- 7.5 The PBAC considered patients classified as having Stage IIIA disease at the time of excision of the primary tumour, and hence not eligible for adjuvant treatment, should be eligible for adjuvant treatment if and when they meet the criteria for Stages IIIB, IIIC or IIID disease and undergo a salvage nodal resection.
- 7.6 Noting that complete lymph node dissection (CLND) at the time of excision of the primary tumour was no longer standard of care for all patients with a positive sentinel lymph node, the PBAC considered that "completely resected disease" would, in practice, include all patients with a wide excision of the primary tumour and either CLND or sentinel lymph node biopsy (or both). Allowing treatment in patients without CLND thus potentially impacts on the applicability of the CA238 trial results to the PBS population. However, it is currently unknown what proportion of patients will forgo a CLND in clinical practice, as although in the MSLT-II trial an improvement in melanoma-specific survival was not demonstrated with immediate CLND, immediate CLND did increase the rate of regional disease control and provided prognostic information in terms of disease in non-sentinel lymph nodes. The PBAC further noted the value of CLND is currently being debated in the clinical literature, and that immediate CLND is standard of care for patients presenting with clinically positive lymph nodes, and therefore more likely to be undertaken in patients with Stage IIIB, IIIC or IIID or Stage IV disease.
- 7.7 The PBAC noted that resubmission again presented an indirect comparison between nivolumab and placebo, with ipilimumab as the common comparator, and used the same clinical trials (CA238: nivolumab versus ipilimumab; and CA029: ipilimumab versus placebo). Although the resubmission claimed that the previous concerns regarding the transitivity and applicability issues between the CA238 and CA029 trials were unlikely to impact the indirect comparison, the PBAC agreed with ESC in considering that a number of issues remained, including the differing durations of ipilimumab treatment and the differing treatment periods.
- 7.8 The resubmission presented updated regression free survival (RFS) data for CA238. This provided an additional six months data, and resulted in a minimum 24 month follow up. The PBAC noted that the indirect hazard ratio for the primary outcome, RFS, remained unchanged to that presented in the July 2018 submission (HR = 0.50; 95% CI: 0.38, 0.65). The PBAC noted that the pre-PBAC response presented very limited

and immature overall survival (OS) data from CA238, which indicated similar OS between nivolumab (■ deaths) and ipilimumab (■ deaths) with 24 months follow-up.

- 7.9 The PBAC considered that the claim that nivolumab was superior to placebo in terms of comparative incremental effectiveness was reasonable in patients with Stage IIIB, IIIC and IIID and Stage IV completely resected melanoma; however, still considered that, due to the immaturity of the data and the use of an indirect comparison, the magnitude of the treatment effect was highly uncertain. The PBAC noted there was insufficient data to assess the benefits and risks or cost-effectiveness of treatment in patients with Stage IIIA disease.
- 7.10 The PBAC again considered that the claim that nivolumab was inferior to placebo in terms of safety was reasonable.
- 7.11 The PBAC noted that the resubmission addressed a number of issues with the economic model that were identified in July 2018, including no longer applying a surrogate relationship between RFS and OS and splitting the disease recurrence health state into locoregional and distant metastatic recurrence. The PBAC also noted that a revised base case was presented in the pre-PBAC response which partially addressed three issues identified by ESC (convergence, utility values and the adjusted OS HR). The PBAC considered that the resultant ICER, \$45,000/QALY - \$75,000/QALY, was high and uncertain. The PBAC:
- considered that, although the revised base case model in the pre-PBAC response converged the RFS, DMFS and OS curves from year 5 to year 30, the period for convergence was too long. The PBAC considered that, as there was a lack of data to determine whether nivolumab delayed or prevented recurrence as well as the overall impact on OS, the model should be conservative and that convergence should occur at 15 years;
  - noted that the OS curve in the observation arm, which was a key driver of the economic model:
    - was informed by Australian data from Haydu (2017). Although the PBAC previously considered that the OS curve, which was based on CA029 had a number of applicability issues, the PBAC considered that the use of this non-trial population introduced a number of additional applicability uncertainties including a different patient population to that identified by the proposed PBS restriction (Stage III patients only with resected and unresectable disease) and, as it included patients diagnosed between 1970 and 2013, a population that most likely did not reflect current SOC;
    - was considered pessimistic by the ESC, particularly when the three year OS (67%) was compared to the observation arm of the COMBI-AD dabrafenib plus trametinib study, Long (2017) (77%). The PBAC noted that in the base case model presented in the resubmission, the OS HR was adjusted by a factor of

0.91 (which resulted in an additional 1.47 life years) to account for improved survival due to current unresectable or metastatic treatments. In response to concerns noted by ESC, the adjustment factor was altered to 0.89 (which resulted in an additional 1.80 life years) in the pre-PBAC response. The PBAC considered that the observation OS curve remained underestimated.

- 7.12 The PBAC, noting that it had previously accepted more conservative ICERs for adjuvant treatment of early breast cancer, considered that a reasonable ICER for adjuvant melanoma therapy would be less than \$15,000/QALY - \$45,000/QALY.
- 7.13 The PBAC noted that the financial implications remained high, at approximately \$110 million per year over the first six years of listing. The PBAC noted that a price reduction, in combination with the exclusion of Stage IIIA patients and adjustments to the grandfathered patients in the pre-PBAC response resulted in lower estimated costs per year than proposed in July 2018. The PBAC still considered that the estimated financial implications were uncertain, particularly with regards to the cost-offsets, which were not well justified, and the proportion of patients initially diagnosed with Stage I or II disease that experience a disease recurrence with resectable Stage III or Stage IV disease.
- 7.14 The PBAC considered that any proposed Risk Sharing Arrangement (RSA) must consider the implications on the current RSA for the use of PD-1 inhibitors in the unresectable or metastatic setting. The PBAC considered that a hard cap that encompassed adjuvant and unresectable use of BRAF/MEK, PD-1 and PDL-1 inhibitors would be appropriate.
- 7.15 The PBAC considered that any future resubmission should be a major submission to allow for evaluation of cost-effectiveness and financial impact. In addition, any additional OS data from CA238 should be presented.
- 7.16 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

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

## **9 Sponsor's Comment**

The sponsor had no comment.