

## 6.07 NIVOLUMAB

**40 mg/4 mL injection, 4 mL vial;  
100 mg/10 mL injection, 10 mL vial,  
Opdivo<sup>®</sup>, Bristol-Myers Squibb**

### 1 Purpose of Application

- 1.1 The submission requested a Section 100 (Highly Specialised Drugs Program), Authority Required (Streamlined) listing for nivolumab as an adjuvant treatment for completely resected Stage III or Stage IV melanoma. Nivolumab has not been considered by the PBAC for this indication previously.
- 1.2 The requested listing was based on cost-utility analysis of nivolumab compared with observation or interferon alfa 2B (IFN $\alpha$  2B). The key components of the clinical issues addressed by the submission are summarised below.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients with completely resected Stage III and IV melanoma.
Intervention	Nivolumab 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks for up to a maximum of 12 months.
Comparator	Main comparator: Observation/watch and wait only as standard of care. This is referred to as 'observation' in this document. Secondary comparator: Interferon alpha 2B (IFN $\alpha$ 2B) Near market comparators: <ul style="list-style-type: none"> <li>• Dabrafenib plus trametinib (DAB+TRAM) in patients with melanoma with a BRAF mutation,</li> <li>• Pembrolizumab.</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>• Recurrence-free survival (RFS)</li> <li>• Overall survival (OS). No OS data were available for the key nivolumab trial. The submission presented an assessment of the validity of RFS as a surrogate outcome for OS.</li> <li>• Safety</li> <li>• Quality-adjusted life-years</li> </ul>
Clinical claim	Nivolumab is superior in terms of effectiveness and moderately inferior in terms of safety compared to placebo as a proxy for standard of care (observation/watch and wait). Nivolumab is superior in terms of effectiveness and safety compared to IFN $\alpha$ 2B. Nivolumab is non-inferior in terms of effectiveness and safety compared to DAB+TRAM. Nivolumab is non-inferior in terms of effectiveness compared to pembrolizumab and equivalent in terms of safety.

Source: Table 18, p2 of the submission.

### 2 Requested listing

Name, restriction, manner of administration, form	Max amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
NIVOLUMAB				
40 mg/4 mL injection, 1 x 4 mL vial	360 mg	11	\$7,560.13 (public hospital)	Opdivo <sup>®</sup>
100 mg/10 mL injection, 1 x 10 mL vial			\$7,703.43 (private hospital)	Bristol-Myers Squibb

<b>Category / Program:</b>	Section 100 - Highly Specialised Drugs <i>Efficient Funding of Chemotherapy</i>
<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

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<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Stage III or Stage IV melanoma that is completely surgically resected
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</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 <i>The patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1,</i> <i>The patient must not have received prior treatment with a PD-1 inhibitor for this condition,</i> AND <i>The patient must not have ocular or uveal melanoma.</i>
<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>Category / Program:</b>	Section 100 - <del>Highly Specialised Drugs</del> <i>Efficient Funding of Chemotherapy</i>
<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 Stage IV melanoma that is completely surgically resected
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction:</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 <del>The treatment must not have exceeded a maximum 12 months total duration.</del> <i>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).</i>

- 2.1 The submission did not propose a Special Pricing Arrangement (SPA). SPAs apply to the current PBS listings for nivolumab for the treatment of renal cell carcinoma and non-small cell lung cancer; however, do not apply to the listing for unresectable Stage III or Stage IV melanoma. There is a Risk Share 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 for completely resected Stage III or Stage IV melanoma, this will likely have downstream consequences for the utilisation of the shared caps between pembrolizumab and nivolumab for unresectable Stage III or Stage IV malignant melanoma (see paragraph 6.67 below).
- 2.2 The requested restriction for initial treatment does not state that patients must not have received prior adjuvant treatment with a programmed cell death-1 (PD-1) inhibitor for this condition. The ESC noted that the submission stated, “it is proposed that patients receive treatment with a PD-1 inhibitor monotherapy on the

PBS only once in the adjuvant melanoma treatment setting.” The ESC further noted that retreatment with nivolumab adjuvant therapy was not included in the economic evaluation or financial analyses. The PBAC and ESC therefore advised that the criterion, “Patient must not have received prior treatment with a PD-1 inhibitor for this condition” be included in the initial treatment restriction.

- 2.3 The ESC noted that the submission stated (pxiv), “in practice, it is anticipated a minority of patients would receive a PD-1 inhibitor as monotherapy in both adjuvant and metastatic settings”. The ESC noted that, if patients were permitted to access PBS-subsidised PD-1 inhibitor therapy more than once in a lifetime, the initial treatment restriction for the current PD-1 inhibitor PBS listings for unresectable Stage III or Stage IV malignant melanoma would need to be changed to allow use in both the adjuvant and unresectable settings. The ESC further noted that the PSCR acknowledged that the impact of sequencing of PD-1 inhibitor therapy from adjuvant to metastatic settings remains an area of uncertainty. The pre-PBAC response noted that a number of agents were listed in both the adjuvant and metastatic settings without supporting trial evidence (e.g. trastuzumab in breast cancer and imatinib in gastro-intestinal stromal tumour). In each case, the PBS restriction for metastatic treatment did not exclude patients who had previously received adjuvant therapy. The pre-PBAC response claimed that patients who relapsed prior to completing of 12 months of nivolumab adjuvant treatment would not be eligible for PD-1 treatment in the unresectable setting under the sequencing restriction proposed in the submission.
- 2.4 The PBAC and ESC advised that the criterion regarding the maximum duration of treatment be amended to ‘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).’
- 2.5 The PBAC noted that the submission did not present any comparative evidence for the effectiveness and safety of nivolumab versus observation (placebo) in the following subsets of patients who would be eligible for PBS-subsidised adjuvant treatment under the requested restriction:
- Patients with completely resected Stage IIIA or Stage IV melanoma;
  - Patients with mucosal or ocular melanoma;
  - Patients who had received prior anti-cancer treatment, other than surgery, for melanoma; and
  - Patients with an Eastern Cooperative Oncology Group (ECOG) performance status >1.

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

### **3 Background**

## Registration status

- 3.1 The approved TGA indication is: nivolumab as monotherapy for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.
- 3.2 The patient population defined in this indication is identical to that for which PBS listing was requested, namely patients with completely resected Stage III or Stage IV melanoma.

## Previous PBAC consideration

- 3.3 This is the first PBAC consideration of nivolumab for the proposed indication.
- 3.4 Nivolumab is currently PBS listed for:
  - Unresectable Stage III or Stage IV malignant melanoma who have not received prior treatment with ipilimumab or a PD-1 inhibitor for this condition;
  - Locally advanced or metastatic non-small cell lung cancer who have progressed on or after prior platinum based chemotherapy;
  - Stage IV clear cell variant renal cell carcinoma who have progressive disease following first-line treatment with a tyrosine kinase inhibitor (TKI) or who have developed intolerance to a TKI of a severity necessitating permanent treatment withdrawal.

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

## 4 Population and disease

- 4.1 Patients who have completely resected Stage III or Stage IV melanoma are at high-risk of developing unresectable disease recurrence, which, in many cases, includes distant metastases. Despite the availability of immunotherapies and targeted therapies for the treatment of advanced and/or metastatic melanoma, unresectable disease remains associated with high mortality. To reduce the risk of relapse post resection, high-risk patients may be considered candidates for adjuvant treatment.\*
- 4.2 Stage III melanoma includes patients with involvement of regional lymph nodes or the presence of in transit or satellite metastases. Under the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual<sup>†</sup>, these patients

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\* The American Joint Committee on Cancer (AJCC) Cancer Staging Manual defines the accepted guidelines for the tumour, node, metastasis (TMN) staging system for melanoma, which relies upon assessments of the primary tumour (T) in terms of tumour thickness and the presence/absence of ulceration, the extent of spread to regional lymph nodes (N), and the presence of distant metastases (M). The information from TNM staging is combined to classify patients into AJCC prognostic stage groups.

<sup>†</sup> Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, 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.

are subdivided into four prognostic sub-stages (Stages IIIA-IIID) depending upon the extent of lymphatic involvement and the characteristics of the primary tumour<sup>‡</sup>. Stage IV disease is defined by the presence of distant metastases and there are no subgroups. The 10-year melanoma specific survival (MSS) rates for Stages IIIA, IIIB, IIIC and IIID were estimated to be 88%, 77%, 60% and 24%, respectively, while the MSS rate in patients with Stage IV disease ranged from 10% to 20%, dependent on the site of metastases and serum lactate dehydrogenase levels. The ESC noted the prognosis varied widely by disease stage and therefore that the benefit:risk ratio of adjuvant nivolumab therapy would also vary by stage, and considered the benefit:risk ratio for earlier stages of melanoma (Stage IIIA/B resected) to be uncertain.

- 4.3 In Australia, IFN $\alpha$  2B is the only systemic treatment approved as adjuvant therapy in the treatment of melanoma. As this treatment offers only a small survival benefit and is associated with potential significant toxicity, it is not specifically recommended for routine use by melanoma treatment guidelines and is used in only a few patients. Therefore, there is an unmet clinical need for these patients.
- 4.4 The proposed clinical management algorithm, as presented in the submission, did not fully capture the possible treatment pathways for patients who have recurrence of disease while receiving, or subsequent to completing, nivolumab as adjuvant treatment. In particular, the algorithm did not adequately describe the likely effect of the availability of nivolumab as adjuvant therapy on the subsequent treatment of patients with recurrent disease who develop unresectable Stage III or Stage IV melanoma (where nivolumab is currently used), nor did it provide the proportion of patients likely to receive each subsequent treatment option. In addition, the algorithm indicated that all patients who develop unresectable Stage III or Stage IV BRAF wild type disease subsequent to nivolumab adjuvant therapy would receive a PD-1 inhibitor as first-line therapy, but the submission subsequently stated that it was anticipated that a minority of patients would receive a PD-1 inhibitor in both the adjuvant and the metastatic settings.
- 4.5 If nivolumab becomes available on the PBS for use as adjuvant therapy, it is likely to alter subsequent management of recurrent disease, especially the use of PD-1 inhibitors as first- or later-line treatment for unresectable Stage III and Stage IV disease. The sponsor's Immuno-Oncology Melanoma Advisory Board indicated that, generally, if recurrence occurs on a certain treatment, that treatment would not be used again. If the recurrence was late (>6 months after discontinuing treatment), the initial treatment could be repeated but prescriber preference is likely to be for other treatment.
- 4.6 The ESC noted that the sponsor proposed patients remain eligible for PD-1 monotherapy in the unresectable setting if they relapse subsequent to completion of

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<sup>‡</sup> Note: both the 6th and 7th editions of the AJCC Cancer Staging Manual, which were used in the clinical trials presented in the submission, only included three Stage III subgroups (Stages III A-C).

nivolumab as adjuvant therapy. However, 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. The pre-PBAC response anticipated that, in practice the number of patients who would receive nivolumab in both settings would be minimal, based on the 6% of patients from trial CA209238 who received adjuvant nivolumab and PDL-1 inhibitor monotherapy in the metastatic setting.

- 4.7 The submission did not estimate the proportion of patients who would not be eligible for PD-1 inhibitor treatment in the unresectable setting due to relapsing prior to the completion of nivolumab as adjuvant treatment. The pre-PBAC response noted that in trial CA209238, [REDACTED] % of patients discontinued treatment with nivolumab prior to completing 12 months of therapy. For these patients the appropriate comparison is the use of nivolumab up front as adjuvant therapy with the use of PD-1 inhibitors to treat unresectable disease in patients who experience recurrence in the absence of adjuvant nivolumab.
- 4.8 The ESC considered that overall survival (OS) data from a randomised trial comparing these two treatment strategies is required to address this issue, i.e. earlier rather than later line use of nivolumab; recurrence-free survival (RFS) will not capture the effect of differences in later lines of therapy. OS data were not available for the key nivolumab trial presented in the submission, and, of patients in the placebo arm of CA184029 who had disease recurrence or died, only 30/323 (9.3%) subsequently received a PD-1 inhibitor.

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

## **5 Comparator**

- 5.1 The submission nominated "observation/watch and wait only as standard of care" as the main comparator, and IFN $\alpha$  2B as a secondary comparator. For clarity, 'observation/watch and wait only' is referred to as 'observation'.
- 5.2 The submission noted that IFN $\alpha$  2B is the only systemic therapy that is TGA approved and reimbursed on the PBS as adjuvant therapy for malignant melanoma (restricted to resected disease with nodal involvement). The main arguments provided in support of the nomination of observation as the main comparator, in preference to IFN $\alpha$  2B, were:
- The sponsor's Advisory Board considered that treatment with IFN $\alpha$  2B is not effective in this indication, and is not used in the Australian setting.
  - PBS statistics suggest that the use of IFN $\alpha$  2B for this indication is minimal.
- 5.3 The above arguments are supported by the new draft Cancer Council Australia clinical practice guidelines on the diagnosis and management of melanoma, which state that adjuvant IFN $\alpha$  2B is not considered standard therapy for most melanoma patients. The guidelines recommend that, for those patients with Stage III melanoma

who are not able to receive dabrafenib in combination with trametinib (DAB+TRAM) or nivolumab (neither of which are TGA approved or PBS listed for resectable Stage III melanoma), IFN $\alpha$  2B may be considered, but given the minimal OS benefit and significant toxicity, routine follow-up is usually preferred<sup>5</sup>.

- 5.4 The PBAC and ESC considered that while the nomination of observation, in preference to IFN $\alpha$  2B, as the main comparator was reasonable, the submission did not adequately consider the downstream consequences of PD-1 inhibitor therapy in the unresectable malignant melanoma setting.
- 5.5 The submission also nominated DAB+TRAM and pembrolizumab as near market comparators. Neither DAB+TRAM nor pembrolizumab are PBS listed or TGA registered for the proposed indication. The comparison of nivolumab with each of these near market comparators relied on a two-step indirect comparison (via ipilimumab and placebo as common references). Only limited details of the trials included in the comparisons were provided. In particular, only data from ClinicalTrials.gov and a press release was available for the trial comparing pembrolizumab and placebo. Meaningful conclusions could not be drawn from these unreliable data.

*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 presented clinical case studies and discussed the natural history of the disease, 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 as it provided a clinical perspective on treating melanoma in the adjuvant setting.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (40), health care professionals (6) and organisations (2) 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 Melbourne Melanoma Project supporting access to nivolumab as an

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<sup>5</sup> Carlino M, Atkinson V, *et al.* What is the role of adjuvant systemic therapy in patients with resected stage II/III melanoma? (Draft) Sydney: Cancer Council Australia; 2018 [updated 16 March 2018; cited 20 March ]. Available from: [https://wiki.cancer.org.au/australia/Clinical\\_question:What\\_is\\_the\\_role\\_of\\_adjuvant\\_systemic\\_therapy\\_in\\_patients\\_with\\_resected\\_melanoma%3F](https://wiki.cancer.org.au/australia/Clinical_question:What_is_the_role_of_adjuvant_systemic_therapy_in_patients_with_resected_melanoma%3F). This site was accessed on 20 March 2018. The draft guidelines are no longer accessible as the consultation period has concluded.

adjuvant treatment for completely resected Stage III or Stage IV melanoma in clinical practice. The PBAC noted that this advice was supportive of the evidence provided in the submission.

- 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, on the basis of phase 3 trial evidence. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for 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.\*\*

### Clinical trials

- 6.5 For the comparison of nivolumab with observation, the submission was based on an indirect comparison of nivolumab and placebo, with ipilimumab as the common reference, via two randomised trials:
- CA209238: 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); and
  - CA184029: 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.
- 6.6 A randomised controlled trial is currently being conducted to determine whether nivolumab in combination with ipilimumab is more effective than nivolumab monotherapy as adjuvant treatment in patients who have had complete resection of Stage IIIB/C/D or Stage IV melanoma<sup>††</sup> (NCT03068455). The estimated primary completion date is November 2020.<sup>‡‡</sup>
- 6.7 Details of the trials presented in the submission are provided in the table below.

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\*\* Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefits that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefits Scale (ESMO-MCBS). *Annals of Oncology*. 2015;26:1547-1573

†† The number of prognostic Stage III groupings was increased from 3 to 4 subgroups (Stages IIIA-IIID) in the 8th edition of the AJCC Cancer Staging Manual.

‡‡ Source: <https://clinicaltrials.gov/show/NCT03068455>

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**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
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.  Weber J, Mandala M, Del Vecchio M, Gogas HJ, et al. Adjuvant nivolumab versus ipilimumab in resected Stage III or IV melanoma.	July 2017  New England Journal of Medicine 2017; 377(19):1824-35.
CA184029	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.  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.  Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in Stage III melanoma with ipilimumab adjuvant therapy.	June 2014  The Lancet 2015; 16(5):522-30.  New England Journal of Medicine 2016; 375(19):1845-55.

Source: Table 37, pp37-38 of the submission.

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

**Table 3: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias**	Patient population	Outcomes	Use in modelled evaluation
<b>Nivolumab vs. ipilimumab</b>						
CA209238	906	R, DB Mean duration of treatment: NIVO: █ doses (SD: 7.94) IPI: █ doses (SD: 1.84) Minimum FU 18 months	Low	Stage IIIB/C or Stage IV melanoma that is completely resected	RFS	Used
<b>Placebo vs. ipilimumab</b>						
CA184029	951	R, DB Mean duration of treatment: IPI: █ doses (SD: 4.32) PBO: █ doses (SD: 4.85) Median FU: 2.7 years (RFS) 5.3 years (OS)*	Low	Stage III cutaneous melanoma that is completely resected	RFS OS	Used

DB = double blind; FU = follow up; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PBO = placebo; R = randomised; RFS = recurrence-free survival; SD = standard deviation

\* 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.

\*\* Risk of bias in the primary outcome (RFS) is low in the individual studies but the indirect comparison of the two trials had a high risk of bias due to the poor transitivity of the two trials.

Source: Compiled during the evaluation based on Table 2, pp8-10 Appendix B to the submission and Table 42, p53 and Table 44, pp55-56 of the submission.

6.9 The ESC noted that the definition of RFS in CA209238 was the time between the date of randomisation and the date of first recurrence (local, regional or distant metastasis), new primary melanoma, or death (whatever the cause), whichever occurs first ; and in CA184029 was the time between the date of randomisation and the date of first recurrence (local, regional or distant metastasis) or death (whatever the cause), whichever occurs first. The ESC noted the use of a composite endpoint

consisting of different health outcomes and different definitions of RFS across the two trials potentially affects the transitivity of the trials used in the indirect comparison. The ESC considered that the relevance and clinical importance of this composite endpoint for the final health outcomes of patients was uncertain and could vary substantially (e.g. implications of local recurrence versus distant metastasis versus death). The pre-PBAC response acknowledged the differences in the definitions of RFS relating to the occurrence of new primary melanoma; however, noted that in CA209238 more new primary melanoma events occurred in the nivolumab arm (1.5% of patients) compared to in the ipilimumab arm (0.9%). The pre-PBAC response claimed that this favoured nivolumab therapy. In addition, as the Kaplan Meier curves for RFS in the ipilimumab arms of the CA184029 and CA209238 trials closed matched, the transitivity issues associated with the difference in definitions were considered marginal.

- 6.10 The risk of bias in the primary outcome of RFS in each individual trial was low. However, for the indirect comparison, the risk of bias was high given the non-randomised nature of comparison.
- 6.11 The indirect comparison and the consequent clinical claim of nivolumab versus observation were based on the outcome of RFS as OS data were not available for CA209238<sup>§§</sup>. The availability of nivolumab for use as adjuvant therapy is likely to alter subsequent management of recurrent disease, especially the use and efficacy of PD-1 inhibitors as first- or later-line treatment for unresectable Stage III and Stage IV disease. Only OS data will capture the overall impact of listing nivolumab as adjuvant therapy on the complete treatment pathway for these patients.

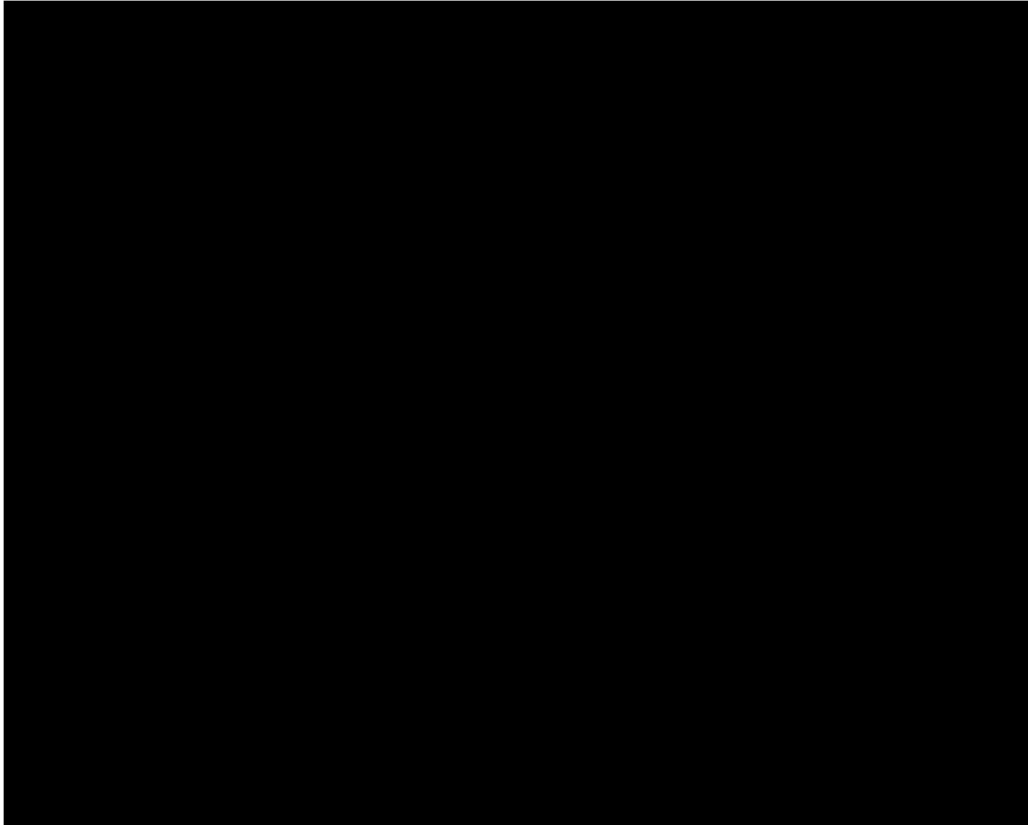
### **Comparative effectiveness**

- 6.12 The Kaplan Meier plots for RFS from studies CA209238 and CA184029 are presented below. Further details are provided in the indirect comparison in Table 5.

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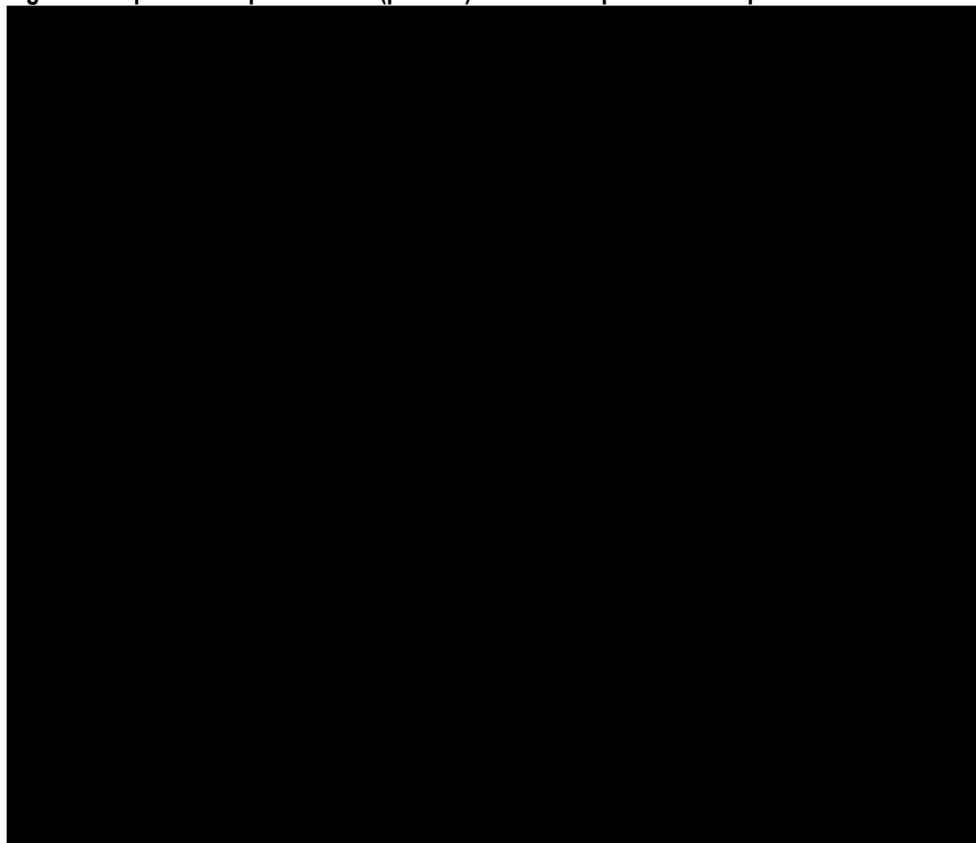
<sup>§§</sup> The final analysis of OS in CA209238 was to be performed at the end of the trial. The estimated trial completion date was the end of November 2019 ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT02388906).

**Figure 1: Kaplan Meier plot for RFS: CA209238 nivolumab vs ipilimumab**



CI = confidence interval; Ipi = ipilimumab; NA = not available; Nivo = nivolumab; RFS = recurrence-free survival  
Source: Figure 19, p71 of the submission.

Figure 2: Kaplan Meier plot for RFS (per IRC): CA184029 ipilimumab vs placebo



CI = confidence interval; IRC = Independent Review Committee; RFS = recurrence-free survival  
Note: the hazard ratio for placebo versus ipilimumab was 1.33 (95% CI: 1.11, 1.56)  
Source: Figure 19, p71 of the submission.

- 6.13 The PBAC noted that the RFS data in CA209238 were still immature. The median RFS was not reached in either of the treatment arms. Therefore, the absolute magnitude of the treatment effect, in terms of the difference in median RFS between the treatment groups, could not be determined.
- 6.14 Visual examination of the Kaplan-Meier plot for RFS suggested that the relative treatment effect was not constant over time, with the curves overlying each other before diverging approximately three months after initiation of therapy (Figure 1 and Figure 2). If the proportional hazards assumption does not hold, the estimated hazard ratio, as a measure of the relative treatment effect or reduction in risk, may be unreliable given the measure's dependency on follow-up time.
- 6.15 The PBAC noted the key transitivity issues across the trials, which are summarised in the table below. It should be noted that, as ipilimumab is the common reference arm, the outcome of interest in CA184029 is the hazard ratio (HR) for placebo compared with ipilimumab (rather than the HR for ipilimumab compared with placebo).

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Table 4: Comparison of key factors that may affect the validity of the indirect comparison

	CA209238 Nivolumab vs ipilimumab	CA184029 Ipilimumab vs placebo	Potential bias in indirect comparison
<b>Duration of follow-up</b>	Minimum 18 months	Median 2.7 years	May affect the validity of the comparison of HRs if the proportional hazards assumption does not hold in either one or both of the trials.
<b>Maturity of data</b>	Interim analysis RFS data immature	Pre-specified primary analysis of RFS RFS data mature	Unclear
<b>Stage of disease<sup>b</sup></b>	Stage IIIB (34.3%), IIIC (46.6%) and IV (18.7%) <sup>a</sup>	Stage IIIA (19.6%), IIIB (44.2%) and IIIC (36.3%)	The inclusion of patients with Stage IIIA melanoma in CA184029 potentially favours placebo over nivolumab. While subgroup analyses are only exploratory, and should be interpreted with caution, the HR for RFS (placebo vs ipilimumab) in Stage IIIA patients was 1.10 (95% CI: 0.69, 1.75; N=186), compared with an HR of 1.33 (95% CI: 1.11, 1.56) in the ITT population. The potential bias due to exclusion of patients with Stage IV melanoma from CA189029 was unclear.
<b>Melanoma types</b>	All melanoma other than ocular/uveal melanoma 84.5% cutaneous	Cutaneous melanoma (excluded mucosal and ocular melanoma or melanoma with unknown origin of the primary).	Unlikely to have major impact on the result of indirect comparison given that the majority of patients in CA209238 had cutaneous melanoma.
<b>Age ≥ 65 years</b>	25.8%	17.6%	Potentially favours placebo over nivolumab. While noting the caveats regarding subgroup analyses above, in CA184029, the HR for placebo vs ipilimumab in patients aged ≥65 years was [redacted] (95% CI: [redacted], [redacted]), compared with [redacted] (95% CI: [redacted], [redacted]) in those aged <65 years.
<b>Duration of treatment</b>	Maximum 12 months	Maximum 3 years	The lower exposure to ipilimumab in the common reference arm in CA209238 compared with CA184029 potentially favours nivolumab over placebo.
<b>Doses received in ipilimumab arm</b> <b>Mean (SD)</b> <b>Median (range)</b>	[redacted] ([redacted]) 4.0 (1-7)	[redacted] ([redacted]) 4.0 (1-16)	

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; RFS = recurrence-free survival; SD = standard deviation

<sup>a</sup> 0.2% of patients in CA209238 were Stage IIIA disease.

<sup>b</sup> Prior to resection

Source: Table 41, p50, Table 42, p42, Table 43, p53, Table 44 pp55-56 of the submission; Tables 1, 2 and 3 Appendix B to the submission; Synopsis and Table S.3.8 CA209238 CSR; Synopsis CA184029.

6.16 The results of the indirect comparison of RFS are provided below.

**Table 5: Results of the indirect comparison for recurrence-free survival**

	CA209238		CA184029	
	Nivolumab N = 453	Ipilimumab N = 453	Ipilimumab N = 475	Placebo N = 476
Follow-up	Minimum 18 months		Median 2.7 years	
Events, n (%)	154 (34.0%)	206 (45.5%)	234 (49.3%)	294 (61.8%)
Median RFS, months (95% CI)	NC	NC (16.6, NC)	26.1 (19.3, 39.3)	17.1 (13.4, 21.6)
12 month RFS rate, % (95% CI)	70.5 (66.1, 74.5)	60.8 (56.0, 65.2)	63.5 (58.9, 67.7)	56.1 (51.5, 60.5)
p-value (log-rank test)	<b>&lt;0.0001</b>		<b>0.0013</b>	
Hazard ratio (95% CI)	Nivolumab vs ipilimumab <b>0.66 (0.53, 0.81)</b>		Placebo vs ipilimumab <b>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)</b>			

CI = confidence interval; HR = hazard ratio; NC = not calculable; RFS = recurrence-free survival

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

**Figures in bold are statistically significant.**

Source: Table 49, p69 and Table 56, p100 of the submission.

6.17 The submission stated that the indirect HR for RFS was highly significantly in favour of nivolumab and represented a 50% risk reduction in recurrence in the nivolumab group compared with the placebo group. The PBAC and ESC considered the submission's claim that nivolumab is superior to placebo in terms of RFS was reasonable. However, given the concerns regarding the transitivity of the trials included in the indirect comparison, and the indirect nature of the comparison, the magnitude of the treatment effect was highly uncertain. In addition, the submission did not assess the proportional hazard assumption in either of the trials. If the proportional hazards assumption does not hold, the estimated HR, as a measure of the relative treatment effect, may be unreliable as it would be dependent on follow-up time.

6.18 The PBAC and ESC noted that there was no direct evidence for OS and considered that the surrogacy of RFS for OS was highly uncertain.

6.19 Both trials assessed quality of life using the European Organisation for the Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C30). In CA209238, there was with no mean change from baseline reaching the minimal clinically important difference of 10 points on a 100-point scale at any time point in global health status, or the individual functioning or symptom scales in either treatment group. In CA184029, during the induction phase, health-related quality of life declines were seen in mean changes from baseline on fatigue and diarrhoea in the ipilimumab group. By week 24, mean scores were within 10 points of baseline for all scales and symptom scores, and remained so throughout the study period. There was a high risk of attrition bias in CA184029 due to differential rates of completion of the questionnaire between the two treatment arms (█% and █% in the ipilimumab and placebo groups, respectively). The submission did not present an indirect comparison of quality of life for nivolumab versus placebo.

## Comparative harms

6.20 A comparison of the key adverse events (AEs) in the randomised trials is presented in the table below.

**Table 6: Summary of key adverse events in the randomised trials**

	CA209238		CA184029	
	Nivolumab N = 452	Ipilimumab N = 453	Ipilimumab N = 471	Placebo N = 474
Duration of follow-up	Minimum 18 months <sup>a</sup>		Median 2.7 years <sup>b</sup>	
Number of doses, mean (SD)	■ (■)	■ (■)	■ (■)	■ (■)
<b>All causality AEs, n (%)</b>				
AE – any grade	438 (96.9%)	446 (98.5%)	465 (98.7%)	432 (91.1%)
Grade 3-4 AE	115 (25.4%)	250 (55.2%)	254 (53.9%)	118 (24.9%)
Serious AE – any grade	79 (17.5%)	183 (40.4%)	254 (53.9%)	119 (25.1%)
Grade 3-4 Serious AE	48 (10.6%)	144 (31.8%)	176 (37.4%)	65 (13.7%)
Discontinuation of study drug due to AE	44 (9.7%)	193 (42.6%)	245 (52.0%)	42 (8.9%)
Any death	44 (9.7%)	45 (9.9%)	122 (25.9%)	160 (33.8%)
Death within 30 days last dose	0	0	1 (0.2%)	0
<b>Drug-related AEs, n (%)</b>				
AE – any grade	385 (85.2%)	434 (95.8%)	443 (94.1%)	282 (59.5%)
Grade 3-4 AE	65 (14.4%)	208 (45.9%)	216 (45.9%)	19 (4.0%)
Serious AE- any grade	24 (5.3%)	141 (31.1%)	216 (45.9%)	10 (2.1%)
Grade 3-4 Serious AE	15 (3.3%)	111 (24.5%)	147 (31.2%)	5 (1.1%)
Discontinuation of study drug due to AE	35 (7.7%)	189 (41.7%)	224 (47.6%)	7 (1.5%)
Death	0	0	5 (1.1%)	0

AE = adverse event; SD = standard deviation

<sup>a</sup> All toxicities were documented for a minimum of 100 days after the last dose of study medication (p35 CA209238 Protocol)

<sup>b</sup> Toxicities were assessed up to 70 days after last dose of study therapy (p34 CA184029 Protocol).

Source: Table 44, pp55-56, Table 51, p78 and Table 52, p79 of the submission.

6.21 The submission presented the results of statistical indirect comparisons for each AE outcome. Nivolumab was associated with statistically significantly more drug-related Grade 3-4 AEs, drug-related Grade 3-4 serious AEs, and drug-related discontinuations due to AEs compared to placebo. There were considerable differences in the proportion of patients experiencing serious AEs and discontinuing study drug due to AEs between the ipilimumab arms of the two trials. This is likely to reflect the difference in the exposure to ipilimumab between the common reference arms of the two trials, and the longer duration of follow-up in CA184029 compared with CA209238.

6.22 The majority of immune-mediated AEs (IMAEs) in the nivolumab group were Grade 1-2. The most frequently reported IMAEs (any grade) were rash (16.2%), and hypothyroidism/thyroiditis (13.9%), while the most frequently reported Grade 3-4 IMAEs were diarrhoea/colitis (2.0%) and hepatitis (2.0%). Other events of special interest within 100 days of the last dose of nivolumab included four subjects with pancreatitis and three subjects with uveitis.

6.23 The most frequent AEs (of any cause) in the nivolumab arm were fatigue (46%), rash (29%), diarrhoea (24%), pruritus (23%), nausea (15%), arthralgia (13%),

musculoskeletal pain (11%), and hypothyroidism (11%). The majority of these AEs were mild to moderate (Grade 1 or 2).

## Benefits/harms

6.24 A summary of the comparative benefits for nivolumab versus placebo is presented in the table below. As discussed above, given the higher exposure to ipilimumab and the longer duration of follow-up in CA184029 compared to CA209238, the magnitude of the relative harms associated with nivolumab compared with placebo cannot be reliably determined.

**Table 7: Summary of comparative benefits for nivolumab and placebo**

<b>Benefits</b>				
<b>Time-to-event outcome RFS:</b>				
	<b>Nivolumab</b>	<b>Ipilimumab</b>	<b>Placebo</b>	<b>HR (95% CI)</b>
<b>CA209238</b>				
Events*, n/N (%)	154/453 (34.0%)	206/453 (45.5%)	-	0.66 (0.53, 0.81)
Median RFS, months (95% CI)	NC	NC (16.6, NC)	-	-
<b>CA184029</b>				
Events**, n/N (%)	-	234/475 (49.3%)	294/476 (61.8%)	0.75 (0.64, 0.90)
Median RFS, months (95% CI)	-	26.1 (19.3, 39.3)	17.1 (13.4, 21.6)	-
<b>Indirect comparison (Nivolumab versus placebo)</b>				0.50 (0.38, 0.65)

\* Minimum follow-up 18 months

\*\* Median follow-up 2.7 years

CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NC = not calculable; NIVO = nivolumab; PBO = placebo; RFS = recurrence-free survival

Source: Table 49, p69 and Table 56, p100 of the submission.

6.25 On the basis of indirectly compared evidence, as presented in the submission, there was a 50% reduction in the risk of recurrence associated with nivolumab over a minimum duration of follow-up of 18 months, compared with placebo over a median duration of follow-up of 2.7 years. However, the magnitude of this estimate is highly uncertain, given the uncertainty regarding compliance with the proportional hazards assumption, the immaturity of the RFS data in CA209238, concerns regarding the transitivity of the trials and the indirect nature of the comparison.

## Clinical claim

6.26 The submission described nivolumab as superior in terms of effectiveness and inferior in terms of safety compared to placebo.

6.27 The PBAC noted that:

- The submission did not provide any evidence for the effectiveness of nivolumab as adjuvant therapy in patients with completely resected Stage IIIA melanoma;
  - CA184029 failed to demonstrate that adjuvant therapy with ipilimumab was associated with any benefit, in terms of either RFS (HR = ■■■■; 95% confidence interval (CI): ■■■■, ■■■■) or OS (HR = 0.98; 95% CI: 0.46, 2.09),

compared with placebo in this relatively low risk subgroup (N=186)<sup>\*\*\*</sup>;

- Both trials excluded patients with ocular melanoma;
- There were no comparative data for the effectiveness of nivolumab versus placebo in patients with completely resected Stage IV melanoma.

- 6.28 The PSCR stated that patients in CA209238 were included based on AJCC 7th edition criteria, and that a review of patients using the newer AJCC 8th edition criteria (conducted by the sponsor for the TGA during the regulatory process) showed [REDACTED] patients who were [REDACTED] and [REDACTED] in the 7th edition would now be mapped as IIIA per the 8th edition. The PSCR argued that therefore, CA209238 does provide data across the stages proposed for adjuvant nivolumab on the PBS. For these patients ([REDACTED] in the nivolumab arm; [REDACTED] in the ipilimumab arm), the HR RFS of nivolumab versus ipilimumab was [REDACTED] (95% CI: [REDACTED], [REDACTED]; p<[REDACTED]). The ESC noted that the reported p-value for this analysis is not consistent with the 95% confidence interval, which includes values [REDACTED]. This was a post hoc subgroup analysis, and randomisation was not stratified by the 8th edition AJCC staging criteria. Baseline demographic and disease characteristics for these patients were not provided. Therefore, the PBAC and ESC advised that results of this analysis should be interpreted with caution.
- 6.29 Given the immaturity of the RFS data in CA209238 and the transitivity issues in the indirect comparison, the PBAC considered that the magnitude of the treatment effect, in terms of RFS, was highly uncertain.
- 6.30 The PBAC noted that there was no direct clinical evidence that the improvement in RFS translates to an improvement in OS once the effect of differences in subsequent lines of therapy in patients with recurrent disease are taken into account. As the availability of nivolumab for use as adjuvant therapy is likely to alter subsequent management of recurrent disease, especially the use of PD-1 inhibitors as first- or later-line treatment for unresectable Stage III and Stage IV disease, the effect of these differences in subsequent therapies on OS also needs to be considered.
- 6.31 The PBAC considered that the claim that nivolumab was superior to placebo in terms of comparative effectiveness was reasonable; however, the magnitude of the treatment effect was highly uncertain.
- 6.32 The PBAC considered that the claim that nivolumab was inferior to placebo in terms of comparative safety was reasonable.

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<sup>\*\*\*</sup> Median follow-up for RFS was 2.7 years, and for OS was 5.3 years. The HR for OS in the intention-to-treat population in CA184029 (ipilimumab versus placebo) was 0.72 (95% CI: 0.59, 0.88)

## Economic analysis

6.33 The submission presented a cost-utility analysis based on the indirect comparison of randomised trials comparing nivolumab with the main comparator observation.

6.34 A summary of the key components of the economic evaluation is presented in the table below.

**Table 8: Summary of model structure and rationale**

Component	Summary
Outcomes	Life years; Quality-adjusted life years. These outcomes are appropriate.
Time horizon	█ years in the model base case. The submission argued that █ was appropriate to capture differences in survival.
Method used to generate results	Cohort analysis using a partitioned-survival approach.
Health states	Recurrence free disease; Recurrent disease; Death.
Cycle length	3 monthly cycles. This is reasonable.
Transition probabilities	No specific transition probabilities are modelled. Health state allocation over time determined by RFS and OS curves. See Table 9 for details.
Discounting	5% for outcomes and costs.
Software	Excel 2016

OS = overall survival; RFS = recurrence-free survival

Source: Table 66, p125 Section 3 of the submission

6.35 The model included three health states – recurrence-free, recurrence and death. The application of static costs and utilities to each health state may not accurately reflect the outcomes of patients treated in the adjuvant setting in terms of both costs and utilities over the time horizon of the model (█ years).

- Recurrence after adjuvant treatment could include a heterogeneous population (e.g. recurrence with local versus distant metastasis etc.) with different final health outcomes. It is unlikely that costs and utilities for the recurrent disease health state will remain static throughout the time horizon of the model.
- The submission has assumed the same costs in each of the treatment arms. As noted earlier, the availability of nivolumab as an adjuvant treatment may alter the subsequent management of recurrent disease, especially the use of PD-1 inhibitors as treatment for unresectable Stage III and Stage IV disease. The model did not capture these potential differences, in terms of either cost or health outcomes.

6.36 The PSCR argued that the population following recurrence is not particularly heterogeneous. It stated that of all recurrences observed in CA209238 approximately █% (█/█) were either regional recurrence (█/█) or distant metastasis (█/355), with this proportion similar across the nivolumab and ipilimumab treatment groups. The PSCR further argued that even if there is heterogeneity within this patient group with ‘different final health outcomes’, the model still captures the appropriate final health outcomes because OS is modelled separately from the individual health states. The ESC considered that the final health outcomes are likely to be different among patients due to the heterogeneous

population following recurrence (refer to paragraph 6.9 above). Moreover, the ESC noted that the issue raised in the commentary was not necessarily whether there were differences in the pattern of recurrence between the two trial arms (which may be difficult to assess, given transitivity issues highlighted above), but that assumptions in the modelling of health outcomes and costs over the time horizon of the model implicitly assumed a homogenous population. Using a single health state to represent disease recurrence may be appropriate if health outcomes and costs over the time horizon of the model are captured correctly.

- 6.37 As overall survival data from CA209238 were not available, the submission presented an assessment of RFS as a surrogate outcome for OS using the framework proposed by the PBAC Surrogate to Final Outcome Working Group.
- 6.38 While RFS may be a valid surrogate for OS in trials comparing IFN with placebo, the PBAC questioned whether the same relationship held for checkpoint inhibitors. The supportive evidence provided in the submission (Suciu, 2018) noted it has not been determined whether RFS correlates with OS for new checkpoint inhibitors when compared with an active drug, as in CA209238 (nivolumab vs ipilimumab) <sup>†††</sup>. Suciu, 2018 also acknowledged that standard of care has improved markedly since the IFN trials were performed, and that the ongoing evolution of treatment algorithms, including sequential use of new treatment modalities, could weaken the surrogacy of RFS for OS, both at the patient and trial levels, as has happened in breast cancer and myeloma. Furthermore, in the IFN trials, post-recurrence treatments were likely to be similar in both the IFN and the placebo arms (i.e. OS would not be confounded by subsequent therapies), whereas the use of nivolumab as adjuvant therapy is likely to modify the use and efficacy of subsequent treatments received by patients with recurrent disease compared to those who do not receive adjuvant PD-1 inhibitor therapy.
- 6.39 The PSCR argued that the validity of RFS as a surrogate for OS was reviewed according to the criteria/framework of the STFWOG Surrogate to Final Outcome Working Group. The ESC acknowledged that the submission appropriately presented a validation study; however; noted that the PSCR did not address the specific issues raised in the commentary regarding the differences between IFN and PD-1 therapy and subsequent lines of therapy. The pre-PBAC response again stated that the relationship between RFS and OS in adjuvant melanoma was well-supported by Suciu, 2018, and that the COMBI-AD (which compared DAP+TRAM to placebo in patients with resected melanoma) and CA184029 trials provided direct evidence that improvements in RFS translate to statistically and clinically significant improvements in OS. The pre-PBAC response also suggested that the indirect comparison between nivolumab and ipilimumab in terms of distant metastases free survival (DMFS) may

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<sup>†††</sup> Suciu S, Eggermont AMM, Lorigan P, Kirkwood JM, Markovic SN, Garbe C, et al. Relapse-Free Survival as a Surrogate for Overall Survival in the Evaluation of Stage II-III Melanoma Adjuvant Therapy. *Journal of the National Cancer Institute*. 2018;110(1):87-96.

offer some insight into OS, given that patients with distant metastases are considered closer in proximity to death (HR = ■■■; 95% CI: ■■■, ■■■). The PBAC and ESC advised that further evidence was required to establish if there was a surrogacy relationship between RFS and OS with PD-1 inhibitor therapy, which may also need to be cancer specific.

- 6.40 On the basis that the regression model derived in Suciu, 2018, which indicated that the risk reduction due to IFN treatment compared with placebo was approximately the same for OS and for RFS, the economic model in the submission has assumed that the HR for OS was the same as the HR for RFS (derived in the indirect comparison of nivolumab versus placebo). This was inappropriate for the reasons outlined above and as it assumed, without adequate justification, that the regression model derived in Suciu 2018 was applicable to the indirect comparison of nivolumab and placebo, via an active common comparator. Not only will the HR for OS reflect the differences between the nivolumab and placebo arms in the subsequent lines of therapy received by patients with recurrent disease, but the baseline risk of the study population in CA209238 varied from that in which the model was derived<sup>+++</sup>. In addition, if the proportional hazards assumption did not apply in either CA209238 or CA184029, the estimated HR for RFS would be dependent on the duration of follow-up.
- 6.41 The submission constructed survival curves for the observation arm based on the placebo arm from CA184029, the melanoma-specific survival data from Balch, 2009 and general population life tables. The submission applied HRs from the indirect comparisons in order to construct the survival curves of nivolumab first two years. The assumptions and data sources for the RFS and OS estimates in the model are summarised in the table below.

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<sup>+++</sup> In contrast to the trials included in the derivation of the regression model, which included patients with resected grade II-III disease cutaneous melanoma, CA209238 included patients with Grade IV disease and with other subtypes of melanoma (e.g. mucosal and acral melanoma).

Table 9: Model inputs for RFS and OS

Component	Observation	Nivolumab
<b>RFS</b>		
Years [redacted]	KM Curves of PBO arm from CA184029	HR = [redacted] was applied [redacted]
Years [redacted]	Extrapolation ([redacted]) of KM curves from PBO arm of CA184029	[redacted]
Years [redacted]	[redacted]	[redacted]
<b>OS</b>		
Years [redacted]	KM curves of PBO arm of CA184029 trial	HR = [redacted] was applied [redacted]
Years [redacted]	[redacted]	[redacted]
Years [redacted]	General population life tables	[redacted]

HR = hazard ratio; KM = Kaplan Meier; MSS = melanoma specific survival; OS = overall survival; PBO = placebo; RFS = recurrence-free survival

Source: compiled during the evaluation based on information provided in Section 3

6.42 The submission did not address the applicability of the trial population to the proposed PBS population in terms of age. The Cancer in Australia 2017 Report indicated that the mean age at melanoma diagnosis in 2013 was 63 years (median 64.6), which is 12 years older than that in CA184029. Therefore the population in the model (mean age 51 years; Stage III patients only based on CA184029) was not applicable to the proposed patient population (mean 63 years at diagnosis; Stage III and Stage IV disease). All else being equal, this will overestimate the RFS and OS for patients compared to the proposed Australian population for the observation arm, consequently overestimating the cost-offsets associated with the treatment of recurrent disease.

6.43 The PSCR argued that age has not been shown to be a determinant of RFS, OS or treatment effect in any of the trial data presented in the submission. It further argued that the submission presented a validation of modelled OS outcomes against real-world evidence in a matched (by stage) population, which showed the model performed well at predicting OS in a real-world patient population.

6.44 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 [redacted] from year [redacted], and that the curve [redacted] year [redacted];

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- 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 remains uncertain.
  - The competing risk of death due to other causes will not be accurately captured in either the RFS or OS curves.
- 6.45 The submission stated that the RFS curve for years [REDACTED] for the observation arm was based on an [REDACTED] 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.
- 6.46 The application of a constant transition probability for recurrence-free survival does not incorporate the increasing competing risk of death from other causes as patients' age. This may overestimate the life years gained from treatment with nivolumab compared to observation.
- 6.47 From year [REDACTED], 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 [REDACTED] would no longer faced the risk of dying<sup>§§§</sup>. This is implausible and biased the results of the model in favour of nivolumab.
- 6.48 Beyond year [REDACTED], the submission used natural history data to inform overall survival. The submission applied the per-cycle hazard from the [REDACTED] year of the melanoma specific survival (MSS) curve from Balch, 2009 (weighted average of all Stage III patients) for years [REDACTED]. The population in Balch, 2009 included patients with both resectable and unresectable disease, which differed from the proposed PBS population. There is likely to be a difference in the overall survival of patients with resectable and unresectable disease. The submission has not adequately justified the applicability of this population to the proposed PBS population of patients with resectable disease, nor explored alternative sources of data for the natural history of the disease for patients with resectable disease. In addition, the treatment options for patients included in Balch, 2009 may not reflect the current clinical practice and therefore the OS outcome reported may not be applicable to either the proposed PBS population or population in the model.
- 6.49 The submission applied an annual cost of \$[REDACTED] for the management of recurrent disease for both arms, based on estimates used in the previous nivolumab and ipilimumab submissions for metastatic melanoma. The 2012 ipilimumab and 2015 nivolumab submissions were for patients with unresectable Stage III or Stage IV malignant melanoma, not a population of patients who have experienced disease recurrence subsequent to adjuvant therapy. It is possible that some patients

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<sup>§§§</sup> The model only allowed changes to the proportion of patients in the RFS health state beyond year 15 where the OS curve lay below the modelled RFS curve. However, this did not occur over the 30 year time horizon of the submission's base case.

experiencing a disease recurrence will have resectable disease, and therefore will not require the same level of monitoring over the time horizon of the model. The annual non-drug cost to manage recurrent disease was likely to be an overestimate, which has contributed to the substantial cost-offset in the comparator arm.

6.50 The PBAC noted that the key drivers of the model, which are summarised in the table below, favoured nivolumab.

**Table 10: Key drivers of the model**

Description	Method/Value	Impact
Time horizon	■ years, this is in conjunction with the estimate of treatment effect and the extrapolation of the treatment effect.	High, favours nivolumab
OS benefit of nivolumab compared with observation	The submission assumed that the HR for OS in the first two years ■	High, favours nivolumab
Extrapolation of the RFS and OS	■	Moderate, favours nivolumab
Disease recurrence management cost (non-drug)	Assumed ■ cost of \$ ■/year.	Moderate, favours nivolumab

HR = hazard ratio; OS = overall survival; RFS = recurrence-free survival

Source: Compiled during the evaluation.

6.51 The recurrent disease health state is likely to represent a heterogeneous population in terms of subsequent health outcomes, with some patients likely to become disease-free after subsequent treatment and others experiencing disease progression. Thus, a single health state representing recurrence, along with static health state costs (based on unresectable Stage III and Stage IV disease) and utilities may not accurately reflect the outcome of subsequent treatment(s) in terms of both costs and utilities over the time horizon of the model.

6.52 The results of the economic evaluation are summarised below.

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Table 11: Results of the stepped economic evaluation: nivolumab vs observation

Step and component	Nivolumab	Observation	Increment
<b>Step 1: Data from placebo arm of CA184029, applying the HR from the ITC to RFS only (2 year time horizon)</b>			
Costs <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
RFS years	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra RFS year gained			\$ [REDACTED]
<b>Step 2: Applying surrogacy relationship for transformation of treatment effect for RFS to OS: HR<sub>RFS</sub> = HR<sub>OS</sub> (2 year time horizon)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYs gained			\$ [REDACTED]
<b>Step 3: Transformation of health states to utility values (2 year time horizon)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Step 4: Extrapolation of model duration to 30 years</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs gained	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/extra QALY gained (base case)</b>			\$ [REDACTED]

<sup>a</sup> This differed from the estimate provided in the submission. The ICER provided in the submission included total costs that were derived from the model which still applied the one-to-one surrogacy of the HR for RFS to OS (as per Step 2).

HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life year; OS = overall survival; QALY = quality-adjusted life year; RFS = recurrence-free survival

Source: Compiled during the evaluation based on information presented in '9.AdjNIVO\_Section3model\_March2018.xlsx'

The redacted table shows ICERs in the range of more than \$200,000/extra RFS year-gained; more than \$200,000/extra LY gained; more than \$200,000/extra QALY gained; and \$15,000/extra QALY gained - \$45,000/extra QALY gained (base case).

6.53 The above table indicated that the extrapolation from [REDACTED] years to [REDACTED] years had a substantial impact on the final results of the economic model. As noted above, the modelled RFS and OS curves were based on an indirect comparison and the subsequently extrapolated survival curves (and the consequent duration for each health state) are highly uncertain.

6.54 Key sensitivity analyses presented in the submission are summarised in the table below.

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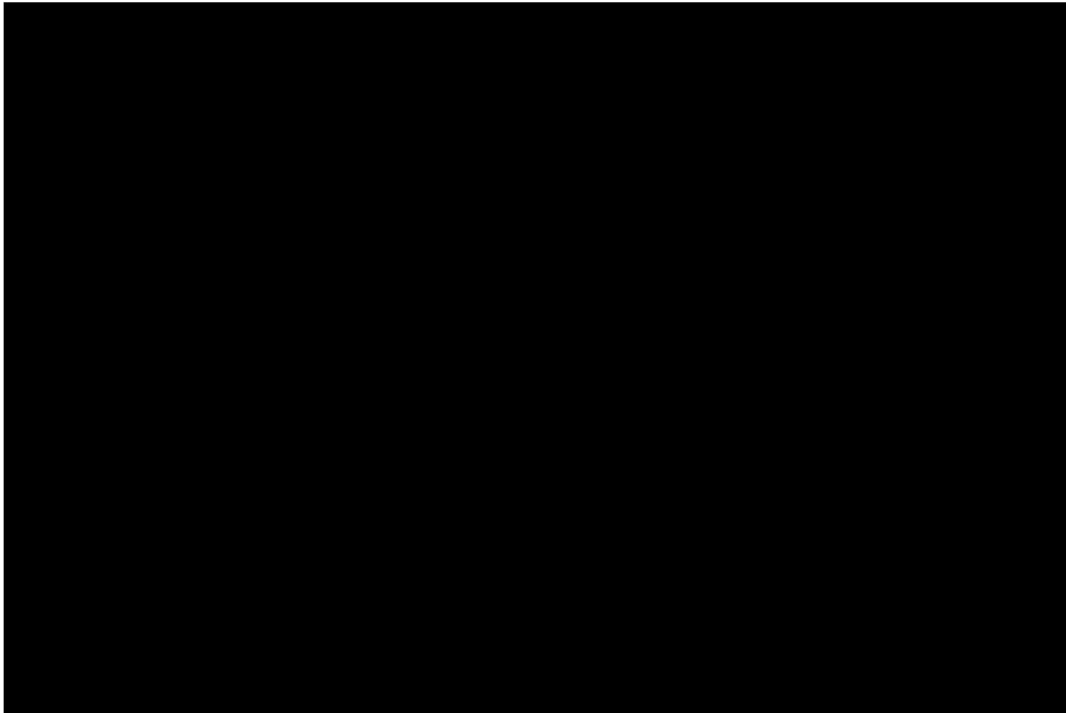
Table: Sensitivity analysis of the economic model

Variable tested (base case)	Sensitivity analysis	Nivolumab vs observation		
		Inc. Costs	Inc. QALYs	ICER
<b>Base case</b>	-	\$ [redacted]	[redacted]	\$ [redacted]
<b>Treatment effect and surrogacy variables</b>				
NIVO HR <sub>RFS</sub> ( [redacted] )	95% LCL [redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	95% UCL [redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	Revised (95% UCL [redacted]) <sup>a</sup>	\$ [redacted]	[redacted]	\$ [redacted]
NIVO HR <sub>RFS</sub> (HR <sub>OS</sub> = HR <sub>RFS</sub> X [redacted])	HR <sub>RFS</sub> = 95% LCL [redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	HR <sub>OS</sub> = [redacted]	[redacted]	[redacted]	[redacted]
	HR <sub>RFS</sub> = 95% UCL [redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	HR <sub>OS</sub> = [redacted]	[redacted]	[redacted]	[redacted]
	Revised: HR <sub>RFS</sub> = 95% UCL [redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	HR <sub>OS</sub> = [redacted] <sup>a</sup>	[redacted]	[redacted]	[redacted]
<b>Extrapolation variables</b>				
Duration of trial based HR before HR = [redacted] ( [redacted] years)	[redacted]	\$ [redacted]	[redacted]	\$ [redacted]
Convergence extrapolation (HR based assumptions until start variable in years, then linear decline in incremental effect until converge end variable in years). No convergence assumed in the base case	[redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	[redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	[redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	[redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	[redacted]	\$ [redacted]	[redacted]	\$ [redacted]
	[redacted]	\$ [redacted]	[redacted]	\$ [redacted]
<b>Model structure</b>				
Model duration ( [redacted] years)	[redacted] years	\$ [redacted]	[redacted]	\$ [redacted]
	[redacted] years	\$ [redacted]	[redacted]	\$ [redacted]
<b>Patient Characteristics</b>				
Patient age (51 years)	[redacted] years	\$ [redacted]	[redacted]	\$ [redacted]
	[redacted] years	\$ [redacted]	[redacted]	\$ [redacted]

<sup>a</sup> The UCL for RFS HR was incorrectly reported in this table as HR = [redacted]. This should have been HR = [redacted].  
 AE = adverse event; HR = hazard ratio; LCL = lower confidence limit; ICER = incremental cost-effectiveness ratio; IFN = interferon; Inc = incremental; IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PBO = placebo; QALY = quality-adjusted life year; RFS = recurrence-free survival; UCL = upper confidence limit  
 Source: Table 96, p166 Section 3 of the submission

6.55 The PBAC noted that the model was variable and sensitive to the modelled treatment effect and time horizon. Setting the RFS and OS curves starting to converge at year five, and completely converge at the end of year 10 resulted in an ICER of \$105,000/QALY - \$200,000/QALY for the comparison of nivolumab versus observation. Setting the time horizon of the model to 10 years (without convergence of the extrapolated curves) resulted in an ICER of \$75,000/QALY - \$105,000/QALY for the comparison of nivolumab versus observation. See Figure 3 below.

Figure 3: ICER (\$/QALY) over the time horizon of the model (nivolumab vs observation)



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

6.56 The PBAC and ESC noted that the significant uncertainty surrounding the magnitude of OS benefit of nivolumab over observation resulted in an uncertain and highly variable ICER. The PBAC and ESC also considered that as the RFS to OS relationship is a key driver of the model, which is then compounded by the application of the 30-year time horizon and the transition probability issues, the base case ICER of \$15,000/QALY - \$45,000/QALY was likely to be significantly underestimated.

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

6.57 Based on a mean (SD) weight of 81.33 (SD: 19.42) kilograms per person (CA209238), 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) 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 (█ doses) as observed in CA209238, assuming 70% will be dispensed for use in a private hospital (based on PBS statistics for ipilimumab, nivolumab and pembrolizumab).

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\*\*\*\* Note: This does not include the \$20 TGA-licensed compounder's fee.

## Estimated PBS usage & financial implications

6.58 This submission was considered by DUSC.

6.59 The submission used an epidemiological approach to estimate the likely extent and use of nivolumab and associated financial implications to the PBS.

6.60 The PBAC considered that the size of the eligible patient population was uncertain. The submission estimated it from the:

- incidence of melanoma, using Australian Institute of Health and Welfare (AIHW) cancer projections 2007-2020 and a simple linear extrapolation of these data to 2024. The PBAC and DUSC noted that the use of incident melanoma estimates to quantify the eligible population is based on diagnosis of primary disease, and does not incorporate those patients diagnosed with earlier stages of disease that subsequently progress to later stages;
- proportion of incident patients diagnosed with Stage III and Stage IV disease based on disease stage of primary melanoma diagnosis from a population of some 17,600 patients from thirteen cancer centres in the USA (Balch, 2001). The PBAC and DUSC considered that the 2001 study, which was in an American population, may differ from the current proposed PBS population; and
- assumption ██████% of Stage III disease will be resectable, ██████% of Stage IV-M1a, ██████% of Stage IV-M1b and ██████% of Stage IV-M1c are surgically resectable.

6.61 The table below describes the estimated use and financial implications of listing adjuvant nivolumab.

**Table 13: Estimated use and financial implications**

	Year 1	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</b>						
Cost to PBS/RPBS	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████
Copayments	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████
Cost to PBS/RPBS less copayments	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████
<b>Estimated financial implications for medicines to treat disease recurrence (avoided)</b>						
Cost to PBS/RPBS	-\$ ██████	-\$ ██████	-\$ ██████	-\$ ██████	-\$ ██████	-\$ ██████
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████
Net cost to MBS <sup>b</sup>	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████
Net cost to PBS/RPBS/MBS	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████

<sup>a</sup> Assuming 2 per patient per year as estimated by the submission.

<sup>b</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)

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme  
Source: Table 106, Table 111, and Table 112 of the submission.

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be more than \$100 million per year.

6.62 The PBAC noted the very high estimated financial impact of listing nivolumab for use the completely resected melanoma population to the PBS and RPBS.

6.63 PBAC and DUSC considered that the cost offsets were overestimated. The main issues were that:

- the submission claimed cost savings to the PBS/RPBS due to patients avoiding recurrence. DUSC considered the current RSA reduces the cost of nivolumab for unresectable melanoma to Government, and the estimated cost offsets are likely to be overestimated;
- the proposed PBS restriction is broader than the eligibility criteria for the CA209238 and CA184029 trials; and
- 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.

6.64 The pre-PBAC response maintained that the cost offsets were reasonable as they were based on the rates of recurrence observed in the nivolumab and placebo arms of the clinical trials and the economic model. The recurrence free survival curves at six years represent a number needed to treat with nivolumab of approximately five in the adjuvant setting to avoid one recurrence. The pre-PBAC claimed that it was estimated that over the first six years of listing that less than 10,000 patients would avoid recurrence; the cost offsets in the analysis reflected this relationship.

### **Quality Use of Medicines**

6.65 The submission described a number of activities to support the quality use of medicines, including:

- Physician education;
- Immuno-oncology preceptorship;
- Peer-to-peer support;
- Nursing and pharmacy in-services
- Risk Management Plan;
- Additional educational materials for awareness and management of immune-related adverse reactions (irARs);
- Educational Materials & Tools; and
- Guidance on Monitoring and Treating Immune Related Adverse Reactions.

## Financial Management – Risk Sharing Arrangements

- 6.66 The submission did not provide any information on potential RSAs for nivolumab as adjuvant treatment in resected melanoma. However, the PBAC noted that there is a 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 nivolumab and pembrolizumab. The sponsors are required to rebate █% to the Commonwealth for costs exceeding the agreed annual expenditure caps. Regardless of whether the PBAC recommends the sequential use of PD-1 inhibitors for different lines of therapy (i.e. in the metastatic setting following the adjuvant setting), the availability of nivolumab in the earlier stages of melanoma will impact on the extent of utilisation and therefore the financial implications for medicines for Stage III or Stage IV unresectable melanoma. These include ipilimumab, nivolumab, pembrolizumab and the BRAF/MEK inhibitors (DAB+TRAM; vemurafenib + cobimetinib). The ESC noted that the market size for unresectable melanoma might also change if nivolumab was PBS-subsidised, due to the cases of recurrent disease avoided.

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

## 7 PBAC Outcome

- 7.1 The PBAC did not recommend listing of nivolumab as an adjuvant treatment for completely resected stage III and IV melanoma. The PBAC acknowledged that there was a high unmet clinical need for effective therapies to reduce the risk of recurrence of resected stage III and IV melanoma, and considered that in some circumstances recurrence was less likely for nivolumab compared to placebo. However the PBAC considered that there was uncertainty in the magnitude of the clinical benefit which resulted in a highly uncertain incremental cost-effectiveness ratio (ICER) and a very high and uncertain estimated financial impact.
- 7.2 The PBAC considered that the nominated comparator, observation, was reasonable in this submission; however, noted that the submission did not adequately consider the place in therapy for nivolumab. The submission did not fully capture the treatment pathways for patients who would have recurrence of disease and the downstream consequences of programmed cell death-1 (PD-1) inhibitor therapy in the unresectable malignant melanoma setting. If nivolumab becomes available for use as adjuvant therapy, it is likely to alter the use of PD-1 inhibitors in the unresectable setting and this impact, particularly in terms of overall survival, remains an area of uncertainty.
- 7.3 The PBAC noted that the submission was based on an indirect comparison between nivolumab and placebo, with ipilimumab (which is not PBS listed for this population) as the common comparator. Two randomised controlled trials were included in the analysis - CA209238, which compared nivolumab to ipilimumab in patients with Stage IIIB/C or Stage IV melanoma, and CA184029 which compared ipilimumab to placebo in patients with Stage III disease. The PBAC questioned the applicability of

the clinical evidence to the requested patient population. The submission requested use for patients with completely resected Stage III and Stage IV melanoma; however, no data for the effectiveness of nivolumab in patients with completely resected Stage IIIA melanoma was presented and no comparative data was presented for patients with Stage IIIA or Stage IV melanoma. In addition to stage of disease, the PBAC considered that there were a number of transitivity issues between the trials, including the duration of follow-up, maturity of the data, average age of the patients and duration of ipilimumab treatment.

- 7.4 The primary outcome of the indirect comparison was recurrence free survival (RFS). The PBAC noted that the data from trial CA209238 were immature and that the median RFS had not yet been reached. The indirect hazard ratio for RFS was 0.50 (95% confidence interval (CI): 0.38, 0.65). The PBAC considered that the submission's claim that nivolumab was superior to placebo in terms of RFS was reasonable. However, the PBAC considered that due to the concerns regarding the transitivity issues between the trials, the immaturity of the data from CA209238 and the indirect nature of the comparison, the magnitude of the treatment effect was highly uncertain. In addition, the PBAC noted that the Kaplan-Meier plots from both trials for RFS suggested that the relative treatment effect was not constant over time, with the curves overlying each other before diverging at three months. The submission did not assess the proportional hazard assumption in either of the trials, and if the proportional hazard assumption does not hold, the estimated HR, as a measure of the relative treatment effect may be unreliable as it would be dependent on follow-up time.
- 7.5 The PBAC considered that the submission's claim that nivolumab was inferior to placebo in terms of safety was reasonable.
- 7.6 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:
- The assumption that the RFS hazard ratio derived from the indirect comparison was a surrogate for the OS hazard ratio. The PBAC and ESC considered that further evidence was required to establish if there is a surrogacy relationship between RFS and OS with PD-1 inhibitor therapy and the quantification of the relationship (see paragraphs 6.38 to 6.40).
  - That the measure of relative treatment effect applied in the model was based on the indirect comparison which was highly uncertain given the immaturity of the RFS data in CA209238 and the transitivity issues.
  - 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 (■ years) as recurrence after adjuvant treatment could include a heterogeneous population (e.g. recurrence with local versus distant metastases) with different final health outcomes and it is unlikely that costs and utilities would remain static over the ■ year horizon.

- The population in the model which was based on CA184029 (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).
- The issues noted by ESC as outlined in paragraphs 6.44 to 6.47 above.

Overall, these issues left the PBAC with considerable uncertainty as to the reliability of the cost-effectiveness of nivolumab adjuvant therapy.

- 7.7 The PBAC considered that although the financial estimates were uncertain, the financial impact was very high (over the range of more than \$100 per year for less than 10,000 patients per year). This was particularly concerning in the context of the uncertain estimate of cost-effectiveness.
- 7.8 The PBAC noted that no clinical evidence was presented for patients with mucosal or ocular melanoma, patients who had received prior anti-cancer treatment, other than surgery, for melanoma, or patients with an Eastern Cooperative Oncology Group (ECOG) performance status of greater than 1. The PBAC recommended that any future proposed PBS listing be amended to reflect these limitations in clinical evidence.
- 7.9 The PBAC recommended that any future submissions be made as Section 100 – Efficient Funding of Chemotherapy program.
- 7.10 The PBAC considered that any future resubmission should be a major submission to allow for evaluation of updated overall survival data, economic modelling and financial impact.
- 7.11 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

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

## **9 Sponsor's Comment**

The sponsor had no comment.