

**7.06 NIVOLUMAB,  
Injection concentrate for I.V. infusion 40 mg in 4 mL,  
Injection concentrate for I.V. infusion 100 mg in 10 mL,  
OPDIVO®,  
Bristol-Myers Squibb Australia Pty Ltd.**

**1 Purpose of Application**

1.1 The re-submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC). The first submission was considered by the PBAC in March 2016.

**2 Requested listing**

2.1 The requested PBS listing is shown below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
NIVOLUMAB			Published price	Opdivo® Bristol-Myers Squibb Australia Pty Ltd (BQ)
40 mg/4 mL injection, 1 x 4 mL vial	360 mg	58	\$ [REDACTED] (Private) <sup>a</sup>	
100 mg/10 mL injection, 1 x 10 mL vial			\$ [REDACTED] (Public) <sup>a</sup>	
			Effective price	
			\$ [REDACTED] (Private) <sup>a</sup>	
			\$ [REDACTED] (Public) <sup>a</sup>	

<sup>a</sup> The dispensed prices for the maximum amount of 360 mg have been updated during the evaluation to include the indexation of fees for the efficient funding of chemotherapy drugs that occurred on 1<sup>st</sup> July 2016<sup>1</sup>. The re-submission proposed a revised special pricing arrangement in which the proposed effective price was reduced compared with that in the previous submission.

<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>Episodicity:</b>	-
<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	<del>Squamous</del> non-small cell lung cancer
<b>PBS Indication:</b>	Locally advanced or metastatic <del>squamous</del> non-small cell lung cancer
<b>Treatment phase:</b>	Initial treatment

<sup>1</sup> Distribution fee \$25.92, diluent fee \$5.14, preparation fee \$103.22, ready prepared dispensing fee \$7.02.

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<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The condition must be squamous type non-small cell lung cancer  AND  Patient must not have received prior treatment with a PD-1 (programmed cell death-1) inhibitor for this condition  AND  Patient must have a WHO performance status of 0 or 1  AND  The treatment must be the sole PBS-subsidised therapy for this condition  AND  The condition must have progressed on or after prior platinum based chemotherapy.</p>
<b>Prescriber Instructions:</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
<b>Administrative Advice:</b>	<p>No increase in the maximum number of repeats may be authorised.</p> <p><i>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</i></p> <p>Special Pricing Arrangements apply.</p>

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
NIVOLUMAB 40 mg/4 mL injection, 1 x 4 mL vial	360 mg	511	Published price	Opdivo® Bristol-Myers Squibb Australia Pty Ltd (BQ)
			\$ [REDACTED] (Private) <sup>a</sup>	
100 mg/10 mL injection, 1 x 10 mL vial			Effective price	
			\$ [REDACTED] (Private) <sup>a</sup>	
			\$ [REDACTED] (Public) <sup>a</sup>	

<sup>a</sup> The dispensed prices for the maximum amount of 360 mg have been updated during the evaluation to include the indexation of fees for the efficient funding of chemotherapy drugs that occurred on 1<sup>st</sup> July 2016<sup>2</sup>. The re-submission proposed a revised special pricing arrangement in which the proposed effective price was reduced compared with that in the previous submission.

<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>Episodicity:</b>	-
<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	Squamous non-small cell lung cancer
<b>PBS Indication:</b>	Locally advanced or metastatic squamous non-small cell lung cancer
<b>Treatment phase:</b>	Continuing treatment

<sup>2</sup> Distribution fee \$25.92, diluent fee \$5.14, preparation fee \$103.22, ready prepared dispensing fee \$7.02.

<b>Restriction Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p><i>The condition must be squamous type non-small cell lung cancer</i></p> <p>AND</p> <p>Patient must have previously been issued with an authority prescription for this drug for this condition</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p><del>Patient must be deriving clinical benefit and tolerating treatment.</del></p> <p><i>Patient must have stable or responding disease.</i></p>
<b>Administrative Advice:</b>	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p> <p><del>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</del></p>

- 2.2 In contrast to the requested restriction in the original submission:
- The revised initial treatment restriction required patients to have a performance score of 0 or 1. This is consistent with the eligibility criteria in the key clinical trial for nivolumab (CA209-017).
  - The continuing treatment restriction contained a note acknowledging early "pseudo-progression" associated with immunotherapy with programmed cell death-1 (PD-1) inhibitors.
- These changes were consistent with the PBAC considerations outlined in the Public Summary Document (PSD) for the original nivolumab submission (paragraph 7.3, 5.06 nivolumab PSD, March 2016 PBAC meeting).
- 2.3 In contrast to the restrictions for PD-1 inhibitors already listed on the PBS:
- The requested restriction for initial treatment did not preclude use of nivolumab in patients who have received prior treatment with a PD-1 inhibitor for the condition. The PSCR (p.1) indicated a willingness to ensure inclusion of specific wording relating to the use of multiple PD-L1 inhibitors.
  - The requested restriction for continuing treatment did not contain the criterion requiring stable or responding disease, which the PBAC previously stated would be necessary (paragraph 7.3, 5.06 nivolumab PSD, March 2016 PBAC Meeting). The PSCR (p.2) agreed to the inclusion of this criterion in the continuing restriction.
- 2.4 As in the original submission, the proposed listing did not restrict nivolumab to patients whose tumours express programmed death ligand-1 (PD-L1). The PBAC previously considered that, as no clear predictive effect of PD-L1 status on the comparative effectiveness of nivolumab versus docetaxel was demonstrated in trial CA209-017, it would be appropriate to allow treatment for patients regardless of PD-L1 status (paragraph 7.3, 5.06 nivolumab PSD, March 2016 PBAC Meeting). Further

evidence is required to fully characterise the value of biomarkers (including PD-L1) for guiding treatment selection in squamous NSCLC.

- 2.5 The re-submission sought listing on the basis of a cost-effectiveness analysis via a direct comparison with docetaxel.

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

### **3 Background**

- 3.1 Nivolumab was registered on the Australian Register of Therapeutic Goods on 12 January 2016 for the following indication relevant to this re-submission:  
Nivolumab, as monotherapy, is indicated for the treatment of locally advanced or metastatic squamous NSCLC with progression on or after prior chemotherapy.
- 3.2 This was the second submission to the PBAC for the requested listing. A previous submission was considered at the March 2016 PBAC meeting.
- 3.3 The PBAC also considered a concurrent re-submission to list nivolumab for non-squamous NSCLC at its November 2016 meeting.
- 3.4 In comparison with the original submission, the re-submission updated some inputs in the economic model and the financial estimates, in response to PBAC's concerns with the original submission.

### **4 Clinical place for the proposed therapy**

- 4.1 NSCLC comprises approximately 15%-25% of the squamous histologic subtype and 75%-85% of the non-squamous histologic subtype. The standard first-line therapy for squamous NSCLC patients is platinum-based doublet chemotherapy, followed by second-line docetaxel. Epidermal growth factor receptor mutations are rare in these patients and so tyrosine kinase inhibitors would rarely be used.
- 4.2 The proposed listing is for patients with squamous NSCLC who have failed platinum-based chemotherapy. Thus, nivolumab would displace docetaxel monotherapy to third-line therapy.
- 4.3 The intended place for nivolumab in the treatment of squamous NSCLC was unchanged from the previous submission.

### **5 Comparator**

- 5.1 The re-submission nominated docetaxel as the main comparator. This was unchanged from the original submission. The PBAC considered that this comparator was appropriate (paragraph 7.4, 5.06 nivolumab Public Summary Document (PSD), March 2016 PBAC Meeting).

*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 speakers offered justifications for some of the assumptions included in the economic model, including the extrapolation method and time horizon, and reiterated the sponsor's willingness to negotiate a risk sharing arrangement (RSA) to manage some of the concerns raised by the ESC.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (5), health care professionals (13) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the value of nivolumab as another treatment option for squamous NSCLC, including the clinically meaningful outcomes for patients and good tolerability of the drug in comparison to docetaxel.
- 6.3 The PBAC noted the input received from the Medical Oncology Group of Australia (MOGA) and the Lung Foundation of Australia, both providing strong support for nivolumab. The input from MOGA highlighted the high clinical value of nivolumab in squamous NSCLC, citing a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) evaluation score for non-curative therapies of 5 in comparison to docetaxel (where 5 and 4 represent the grades with substantial improvement)<sup>3</sup>.

### ***Clinical trials***

- 6.4 The re-submission was based on one open-label head-to-head randomised controlled trial (CA209-017: N=272) comparing nivolumab with docetaxel in previously treated patients with locally advanced or metastatic squamous NSCLC. This trial formed the basis of the clinical evidence in the original submission, which provided results for both 10.6 months and 18 months minimum follow-up (database locks December 2014 and August 2015, respectively). Updated data from the February 2016 database lock (24 months minimum follow-up) were provided in the re-submission.
- 6.5 Details of the trial presented in the re-submission are provided in the table below.

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<sup>3</sup> Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 26:1547-73, 2015

**Table 1: Trial and associated reports presented in the re-submission**

Trial ID	Protocol title / Publication title	Publication citation
<b>Direct randomised trial</b>		
CA209-017	<p>Clinical study report CA209-017: An open-label randomized phase III trial of bms-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC) – (based on database lock 15 December 2014 - minimum follow-up of 10.6 months).</p> <p>Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus docetaxel in advanced squamous cell non-small cell lung cancer.</p> <p><u>Abstract</u></p> <p>Reckamp K et al. Phase 3, Global, Randomized trial (Checkmate 017) of nivolumab vs ,docetaxel in advanced squamous (SQ) cell non-small cell lung cancer (NSCLC) - (database lock of August 2015 - minimum follow-up of 18 months).</p> <p><u>Poster presentation</u></p> <p>Borghaei H, Brahmer J, Horn L, et al. Nivolumab vs docetaxel in patients with advanced NSCLC: CheckMate 017/057 2-year update and exploratory cytokine profile analyses.</p>	<p>February 2015</p> <p>New England Journal of Medicine 2015; 373 (2):123-132.</p> <p>16th World Conference on Lung Cancer. September 6 – 9. 2015. Denver, USA.</p> <p>American Society of Clinical Oncology 2016 Annual Meeting; June 3-7, 2016; Chicago.IL, USA.</p>

Source: Table 11, p18 of the re-submission.

6.6 The key features of the direct randomised trial are summarised in the table below.

**Table 2: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
<b>Nivolumab 3 mg/kg Q2W vs. docetaxel 75mg/m<sup>2</sup> Q3W</b>						
CA209-017	272	<p>R, OL</p> <p>Database lock December 2014 (follow-up 10.6 months),</p> <p>Database lock August 2015 (follow-up 18 months)</p> <p>Database lock February 2016 (follow-up 24 months)</p>	<p>Low for OS</p> <p>High for AEs and QoL.</p>	<p>Patients (unselected for PD-L1 status) who had failed platinum-based chemotherapy</p>	<p>Overall survival</p>	<p>Used</p>

AEs = adverse events; OL = open label; OS =overall survival; PD-L1 = programmed death ligand-1; R = randomised; Q2W = every 2 weeks; Q3W = every 3 weeks; QoL = quality of life.

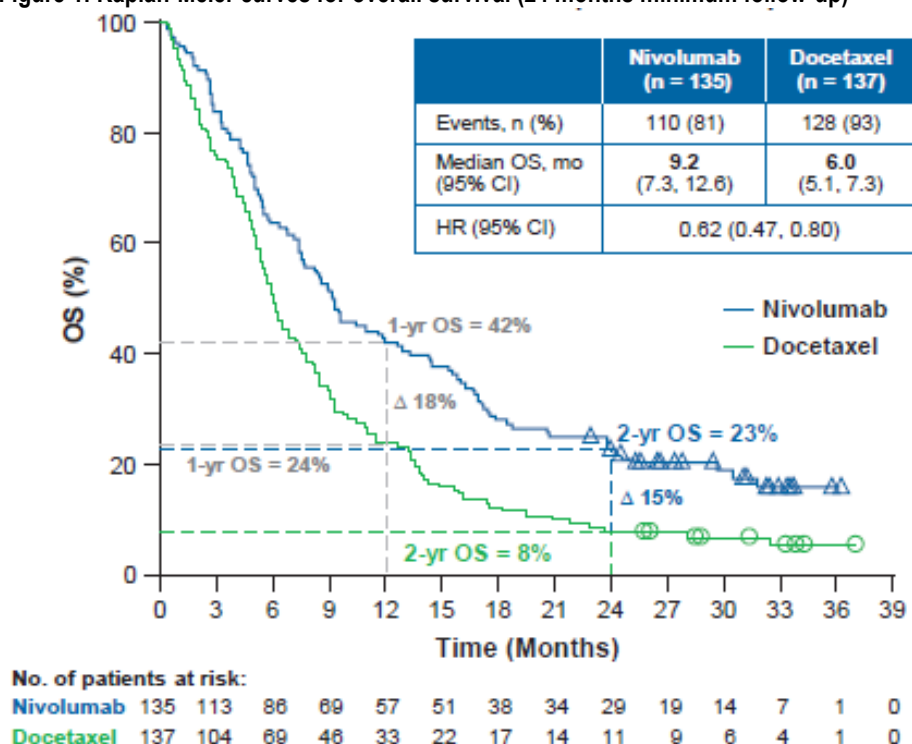
Source: compiled during the evaluation.

6.7 The PBAC previously noted that the key clinical trial, CA209-017, directly compared nivolumab and docetaxel, and the risk of bias was low for the outcome of overall survival (OS) (paragraph 7.5, 5.06. nivolumab PSD, March 2016 PBAC Meeting). Due to the open-label design of the trial, it is possible that the observed rate of immune-related adverse events (AEs) may have been affected by investigator, clinician and patient knowledge of treatment allocation.

### **Comparative effectiveness**

6.8 The Kaplan-Meier curves for OS, based on the updated results from trial CA209-017 (24 months minimum follow-up), are presented below in Figure 1.

Figure 1: Kaplan-Meier curves for overall survival (24 months minimum follow-up)



CI = confidence interval; HR = hazard ratio; OS = overall survival  
Source: Figure 1, p21 of the re-submission.

6.9 Table 3 compares the updated OS results, based on the 24 months minimum follow-up data, with those presented in the original submission (18 months minimum follow-up).

Table 3: Overall survival results from Trial CA209-017

Source	Reckamp et al (2015) Database lock August 2015		Borghaei et al (2016) Database lock February 2016	
	18 months		24 months	
Minimum follow-up	Nivolumab N=135	Docetaxel N=137	Nivolumab N=135	Docetaxel N=137
Number of events, n (%)	103 (76.3)	122 (89.1)	110 (81.5)	128 (93.4)
Median, months (95% CI)	9.2 (7.3, 12.6)	6.0 (5.3, 7.4)	9.2 (7.3, 12.6)	6.0 (5.1, 7.3)
	Nivolumab vs docetaxel		Nivolumab vs docetaxel	
Stratified HR (95% CI)	0.62 (0.48, 0.81)		0.62 (0.47, 0.80)	
Stratified log-rank	p = 0.0004		NR	

CI = confidence interval; HR = hazard ratio; NR = not reported.  
Source: Table 12, p22 of the re-submission.

6.10 The updated results were similar to those presented in the original submission and did not alter any of the previous conclusions regarding the comparative effectiveness of nivolumab versus docetaxel in patients with squamous NSCLC.

6.11 The PBAC previously noted the incremental benefit in median overall survival of 3.2 months. The PBAC noted however, that the incremental benefit in median progression-free survival (PFS) was 0.7 months (paragraph 7.6, 5.06 nivolumab PSD, March 2016 PBAC Meeting).

- 6.12 The PBAC considered that, in contrast to the corresponding trial in non-squamous NSCLC, trial CA209-017 did not support any conclusion of treatment effect variation by PD-L1 status (paragraph 7.7, 5.06 nivolumab PSD, March 2016 PBAC Meeting).

### Comparative harms

- 6.13 Table 4 summarises the updated safety data (minimum follow-up of 24 months) for nivolumab compared with docetaxel in CA209-017.

Table 4: Summary of treatment-related AEs (24 months minimum follow-up)

	Nivolumab n (%) N=131	Docetaxel n (%) N=129	Relative risk (95% CI)	Risk difference (95% CI)
<b>Treatment related AEs</b>				
Any grade	80 (61)	112 (87)	<b>0.70 (0.60, 0.82)</b>	<b>-0.26 (-0.36, -0.16)</b>
Grade 3-4	10 (8)	72 (56)	<b>0.14 (0.07, 0.25)</b>	<b>-0.48 (-0.58, -0.38)</b>
<b>Treatment-related AE leading to discontinuation</b>				
Any grade	8 (6)	13 (10)	0.61 (0.26, 1.41)	-0.04 (-0.11, 0.03)
Grade 3-4	5 (4)	8 (6)	0.62 (0.21, 1.83)	-0.02 (-0.08, 0.03)
Treatment-related deaths	0	3 (2) <sup>a</sup>	-	-0.02 (-0.05, 0.00)
<b>Most frequent treatment-related AEs of any grade (≥10% of patients)</b>				
Fatigue	21 (16)	43 (33)	<b>0.48 (0.30, 0.76)</b>	<b>-0.17 (-0.28, -0.07)</b>
Asthenia	14 (11)	18 (14)	0.77 (0.40, 1.47)	-0.03 (-0.11, 0.05)
Decreased appetite	14 (11)	25 (19)	0.55 (0.30, 1.01)	-0.09 (-0.17, 0.00)
Nausea	12 (9)	30 (23)	<b>0.39 (0.21, 0.73)</b>	<b>-0.14 (-0.23, -0.05)</b>
Diarrhoea	10 (8)	26 (20)	<b>0.38 (0.19, 0.75)</b>	<b>-0.13 (-0.21, -0.04)</b>
Vomiting	4 (3)	14 (11)	<b>0.28 (0.10, 0.83)</b>	<b>-0.08 (-0.14, -0.02)</b>
Anaemia	3 (2)	28 (22)	<b>0.11 (0.03, 0.34)</b>	<b>-0.19 (-0.27, -0.12)</b>
Myalgia	3 (2)	13 (10)	<b>0.23 (0.07, 0.78)</b>	<b>-0.08 (-0.14, -0.02)</b>
Neutropenia	1 (1)	43 (33)	<b>0.02 (0.00, 0.16)</b>	<b>-0.33 (-0.41, -0.24)</b>
Peripheral neuropathy	1 (1)	15 (12)	<b>0.07 (0.01, 0.49)</b>	<b>-0.11 (-0.17, -0.05)</b>
Alopecia	0	28 (22)	0	<b>-0.22 (-0.29, -0.15)</b>
Febrile neutropenia	0	14 (11)	0	<b>-0.11 (-0.16, -0.05)</b>

AE = adverse event; CI = confidence interval

<sup>a</sup> Treatment-related deaths were due to interstitial lung disease, pulmonary haemorrhage and sepsis.

**Bolded figures indicate statistically significant difference**

Source: Tables 13 and 14, p24 of the re-submission

- 6.14 Between the one- and two-year data cut-offs, four patients discontinued nivolumab treatment: one each due to pneumonitis, colitis and increased transaminase, and one due to autoimmune hepatitis, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase, and increased blood lactate dehydrogenase. Due to these additional AEs, there was no longer any statistically significant difference between the treatment groups in the incidence of treatment-related AEs leading to discontinuation. Otherwise, the updated safety data were consistent with those presented in the previous submission.
- 6.15 In regard to the original submission, the PBAC noted the more favourable AE profile of nivolumab for drug-related severe AEs (≥Grade 3), specifically Grade 3-5 neutropenia, compared with docetaxel (paragraph 7.8, 5.06 nivolumab PSD, March 2016 PBAC Meeting).

- 6.16 The risk of serious immune-related AEs associated with nivolumab may be higher in clinical practice than in a clinical trial setting where there is likely to be a heightened awareness and recognition of immune-related AEs, resulting in early intervention before such events progress to a more severe grade.
- 6.17 On 12 August 2015, the nivolumab Company Core Data Sheet was updated with a new warning for immune-related rash, including fatal toxic epidermal necrolysis, and encephalitis, based on cases identified during routine pharmacovigilance signal detection activities. In the March 2016 PSD for nivolumab for non-squamous NSCLC, the ESC noted that the AE of fatal encephalitis is linked to nivolumab, and that a TGA condition of registration was provision of the results of the enhanced pharmacovigilance study of immune-related encephalitis, mandated by the US Food and Drug Administration (paragraph 6.18, 5.07 nivolumab PSD, March 2016 PBAC Meeting).

### ***Benefits/harms***

- 6.18 As the updated results from the database lock in February 2016 were similar to the results from the previous database locks, the benefits/harms of nivolumab and docetaxel were unchanged from the evaluation of the original submission.
- 6.19 The following summary of benefits and harms for nivolumab versus docetaxel is reproduced from the PBAC's March 2016 consideration:
- 6.20 On the basis of the direct evidence presented by the submission, for every 100 squamous NSCLC patients (unselected for PD-L1 expression) treated with nivolumab in comparison to docetaxel:
- Approximately 15 additional patients would be expected to be alive at 18 months. There was a 3.2 month difference in median OS time favouring patients treated with nivolumab over those treated with docetaxel;
  - Approximately 17 fewer patients would experience a drug-related Grade 3 / 4 serious AE and 29 fewer patients would experience drug-related Grade  $\geq 3$  neutropenia, but 5 more patients would experience endocrine-related AEs.

### ***Clinical claim***

- 6.21 The PBAC previously accepted the claim of superior comparative effectiveness and superior comparative safety of nivolumab over docetaxel for the treatment of locally advanced or metastatic squamous NSCLC (paragraphs 7.6 and 7.8, 5.06 nivolumab PSD, March 2016 PBAC Meeting).
- 6.22 As previously, the PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.23 As previously, the PBAC considered that the claim of superior comparative safety was reasonable.

### ***Economic analysis***

- 6.24 The economic evaluation was a Markov model with three health states – progression-free, post-progression and death. The model structure was unchanged

from the previous submission, apart from the time horizon being reduced to 7.5 years from 10 years. The model structure and rationale are presented in the table below.

**Table 5: Summary of model structure and rationale**

Time horizon	7.5 years in the model base case versus 18 months in the trial
Outcomes	LYs and QALYs
Methods used to generate results	Markov model with three health states (progression-free, progressed and death). Cohort expected value analysis.
Cycle length	Three weeks
Transition probabilities	Trial-based Kaplan-Meier PFS and OS curves as well as extrapolated PFS and OS curves
Discount rate	5% per annum for costs and outcomes
Software package	Excel 2010

LYs = life years; OS = overall survival; PFS = progression-free survival; QALYs = quality-adjusted life years

Source: Table compiled during the evaluation

6.25 The key drivers of the model are summarised below.

**Table 6: Key drivers of the model**

Description	Method/Value	Impact
Time point of extrapolation	Median time to censoring	Moderate, favours nivolumab
Method of extrapolation	Log-logistic distribution for PFS and OS in both arms, assuming continued treatment effect until Year 5, with convergence of survival curves occurring from Year 5 to Year 7.5	Moderate, favours nivolumab
Time horizon	7.5 years; assumed from 18 month trial duration	Moderate, favours nivolumab
Ongoing disease management costs for pre-progression disease	The re-submission assumed that during the pre-progression period, patients treated with nivolumab would require 60% of the disease management costs of those treated with docetaxel, based on a survey of the sponsor's Advisory Board members.	Moderate, favours nivolumab
Utility value	CA209-017 trial-based utility data	Low, favours nivolumab
Duration of nivolumab treatment	CA209-017 mean trial-based treatment duration – i.e. truncated with respect to resource use	Low, favours nivolumab

OS=overall survival; PFS=progression-free survival

Source: compiled during the evaluation.

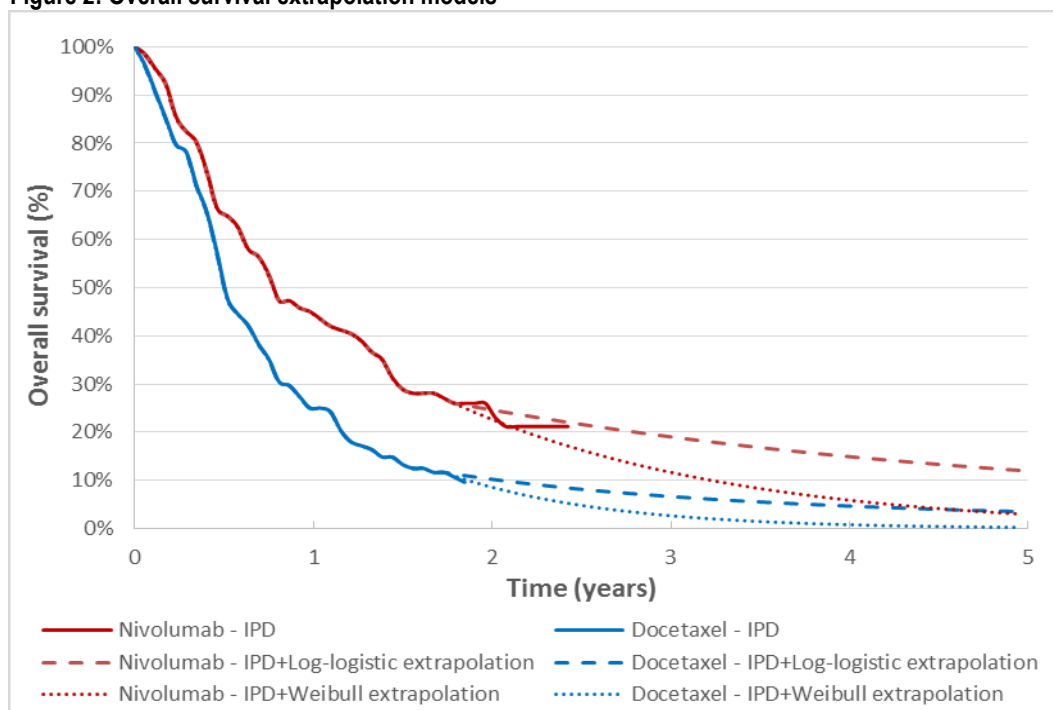
6.26 Although the updated survival results from the February 2016 database lock in CA209-017 (24 months minimum follow-up) were provided in the re-submission, they were not used in the revised economic evaluation. Instead, the survival data from an earlier database lock (August 2015) were applied to the model, unchanged from the economic evaluation in the original submission. The PSCR (p.4) provided the results of the modelled economic evaluation using the updated trial data at the February 2016 database lock. The ESC noted that using survival data from the extended follow-up database lock had minimal effect on the ICER when the log-logistic extrapolation was applied, but noted that PSCR did not use these extended data to either re-examine the basis for selecting between the log-logistic and Weibull based extrapolations, or present the Weibull-based ICER with extended data.

6.27 As in the original submission, the re-submission used three methods to derive the time point from which to extrapolate the Kaplan-Meier OS and PFS curves for the comparative arms. In the base case of the model, the re-submission used median time to censoring based on the reverse Kaplan-Meier methodology (in which

censoring was an endpoint and death was considered as a censored observation (Schemper and Smith 1996, provided in the re-submission)). Median duration of follow-up (i.e. median time trial subjects were observed in CA209-017) and the end of available Kaplan-Meier curves were used in sensitivity analyses.

- 6.28 The re-submission assumed that, after the point of extrapolation, the PFS and OS curves would follow the chosen parametric function continually until Year 5, with convergence of survival curves occurring from 5 years to the end of the time horizon at 7.5 years. The ESC considered that this assumption was not adequately justified given the absence of robust longer-term survival data beyond 2 years for the proposed PBS population.
- 6.29 As in the original submission, the re-submission chose log-logistic parametric distributions for extrapolation of both OS and PFS in both arms. At the March 2016 PBAC meeting, the Committee noted the concern raised by the Commentary that the extrapolation using log-logistic models was more optimistic than that using Weibull models in predicting OS and PFS for both treatment arms. The ESC stated that the use of Weibull function for extrapolation would have been more conservative (paragraph 6.24, 5.06 nivolumab PSD, March 2016 PBAC Meeting). The PSCR (p.2) asserted that the log-logistic method of extrapolation is a more appropriate method of long-term extrapolation for immunotherapy agents than the Weibull distributions, due to the following reasons:
- visual inspection of the curves indicate that log-logistic curves are of better fit than the Weibull curves. The ESC disagreed with this observation, especially with regard to the OS curves (see Figure 2) and noted that a similar graph of curves for the extended follow-up to the February 2016 database lock had not been presented.
  - the AIC for the log-logistic curves indicate that they are more appropriate to use than Weibull curves for both nivolumab and docetaxel. The ESC noted that the reported AICs could not be located in the resubmission and were also not reported for the extended follow-up to the February 2016 database lock.
  - long-term data available for OS in CA209-017 and CA209-003 is better represented by the log-logistic curves than Weibull curves.
  - the Weibull distribution does not allow for non-zero hazards, contrary to the sharp initial decline observed for immune-oncology agents. The ESC considered that the purpose of adopting a curve of best fit against the available evidence is to project these curves beyond the available evidence to inform the extrapolation. Accordingly less weight should be given to the early shape of the curve representing the sharp initial decline.
- Overall, the ESC maintained its previous view that the Weibull model function would be the preferred method of extrapolation for both treatment arms.

Figure 2: Overall survival extrapolation models



IPD = individual patient data

Note: IPD from trial CA209-017 at the August 2015 database lock (18 months minimum follow-up)

Source: Graph constructed during the evaluation (Figure C.2.2.1 of the Commentary)

- 6.30 A time horizon of 7.5 years was used in the base case of the model, in comparison with a 10-year time horizon in the original submission. The PBAC considered that a 5-year time horizon was more appropriate (paragraph 7.9, 5.06 nivolumab PSD, March 2016 PBAC meeting). The PSCR (p.2,3) argued that the data provided in the resubmission supported use of a longer time horizon and that the resubmission “had already reduced the time horizon from 10 years to 7.5 with convergence in an attempt to meet the PBAC halfway”. At its March 2016 meeting, the PBAC noted that the age of the trial population may not be representative of the eligible Australian population, which was likely to be older, and therefore the extent of overall survival gain would be less (see Figure 3). The ESC considered that this would also suggest that 5 years was a more appropriate time horizon.

**QALY Figure 3: Results of prespecified subgroup analyses of CA209-017, including age**

Source: Figure S2 of Supplementary Appendix to: Brahmer J, et al. N Engl J Med 2015;373:123-35.

- 6.31 The ESC advised that if the Weibull extrapolation was used, it would likely mitigate some of the issues regarding the time horizon as these curves converge at around 5 years.
- 6.32 The re-submission updated the average duration of therapy for nivolumab, which was [redacted] infusions, based on the 2-year minimum follow-up data of CA209-017. At the 2-year analysis in CA209-017, 8% (10/131) of subjects were continuing nivolumab treatment, compared with 0% (0/129) in the docetaxel arm. Given that the model extrapolated health outcomes beyond the trial period, the treatment duration for nivolumab should have been extrapolated correspondingly. Using trial-based (i.e.

truncated) treatment durations underestimated the costs of nivolumab, but not of docetaxel, and biased the results of economic evaluation in favour of nivolumab. The ESC considered, as previously, that if the model extrapolates health outcomes to the end of the time horizon, then it should also extrapolate the corresponding costs of treatment linked to those health outcomes.

- 6.33 The re-submission assumed that patients treated with nivolumab would require 60% of the health care resources of those treated with docetaxel, based on opinion from eight members of the sponsor's Advisory Board. The representativeness of the expert opinion was uncertain. The cost reduction associated with pre-progression disease management in the nivolumab arm compared with the docetaxel arm was likely to be overestimated (favouring nivolumab). The previous submission assumed that patients treated with nivolumab would require 80% of the health care resources of those treated with docetaxel. The PBAC noted that relying on only one clinician's opinion in deciding the pre-progression resource use in the nivolumab arm was inappropriate and favoured nivolumab (paragraph 6.27, 5.06 nivolumab PSD, March 2016 PBAC meeting). The PSCR (p.3) asserted that the Advisory Board is a representative sample of clinicians and this assumption is reasonable, however the ESC did not agree that this was adequately justified. Further, the ESC considered that not all pre-progression costs related to adverse events and that it was therefore inappropriate to assume that the other health resource costs would reduce by the same proportion as the costs for management of adverse events.
- 6.34 Utilities applied in the revised economic model were derived from CA209-017 and remained unchanged from the previous submission. At the March 2016 meeting, the PBAC noted that the sample of respondents to the European quality of life 5-dimensions 3-levels (EQ-5D-3L) questionnaires was small, especially at the later stages of the trial. The effect of a healthier cohort providing quality of life data (and sicker patients not responding) may be present and the utility values, particularly for progressive disease, may be overestimated.
- 6.35 The results of the economic evaluation were revised during the evaluation, by incorporating the updated Efficient Funding of Chemotherapy (EFC) fees. The revised results of economic evaluation are summarised below.

Table 7: Revised results of economic evaluation<sup>a</sup>

	Nivolumab	Docetaxel	Increment
<b>Economic evaluation within trial duration<sup>b</sup></b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	1.118	0.730	0.388
QALYs	0.832	0.501	0.331
<b>Incremental cost/LY gained</b>			\$ [REDACTED]
<b>Incremental cost/QALY gained</b>			\$ [REDACTED]
<b>Modelled economic evaluation (extrapolation to 7.5 years)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	1.615	0.950	0.665
QALYs	1.190	0.646	0.543
<b>Incremental cost/LY gained</b>			\$ [REDACTED]
<b>Incremental cost/QALY gained</b>			\$ [REDACTED]

LY = life year; QALY = quality-adjusted life year

<sup>a</sup> Results of economic evaluation were revised by taking into account the Efficient Funding of Chemotherapy fees.

<sup>b</sup> No extrapolation but quality of life data and the cost of disease management (both pre- and post-progression) have been

included.

Source: Results of economic evaluation re-calculated during the evaluation

The redacted table above shows that the incremental cost of nivolumab vs docetaxel for the trial duration was \$105,000 - \$200,000 per life year (LY) gained and \$105,000 - \$200,000 per quality-adjusted life year (QALY) gained, and when extrapolated to 7.5 years, was \$75,000 - \$105,000 per LY gained and \$75,000 - \$105,000 per QALY gained.

- 6.36 The extrapolation of trial survival data had the most effect on the results of economic evaluation. Incremental life years and quality-adjusted life years increased by 64%-71%, from the trial observation to the modelled estimates; whereas the incremental costs increased to a lesser extent. The incremental cost-effectiveness ratio (ICER) for nivolumab versus docetaxel reduced by almost one-third when trial results were extrapolated to 7.5 years.
- 6.37 The Pre-PBAC Response explored the effect of an RSA in which the calculation of the annual expenditure caps limits the cost of nivolumab per patient to that resulting from ■ administrations, resulting in an ICER of \$45,000/QALY - \$75,000/QALY.

**Table 8: Results of key sensitivity analyses**

Label	Model parameter	\$/LY	\$/QALY
<b>Base case</b>	<b>Base case</b>	\$ [REDACTED]	\$ [REDACTED]
SA.1: OS and PFS	Lower confidence limits	\$ [REDACTED]	\$ [REDACTED]
	Upper confidence limits	\$ [REDACTED]	\$ [REDACTED]
SA.2: Point of extrapolation	Median duration of follow-up	\$ [REDACTED]	\$ [REDACTED]
	End of available data	\$ [REDACTED]	\$ [REDACTED]
SA.3: Method of extrapolation	Log-logistic for nivolumab and Weibull for docetaxel	\$ [REDACTED]	\$ [REDACTED]
	Weibull for both PFS and OS in both arms <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]
SA.4: Time horizon	5 years	\$ [REDACTED]	\$ [REDACTED]
	3 years	\$ [REDACTED]	\$ [REDACTED]
SA.5: Utility values	Respective nivolumab and docetaxel utility values <sup>b</sup>	\$ [REDACTED]	\$ [REDACTED]
	Overall utility values in both arms	\$ [REDACTED]	\$ [REDACTED]
	Utility for progressive disease assumed to be 0.59 in both arms <sup>a,c</sup>	\$ [REDACTED]	\$ [REDACTED]
SA.6: Nivolumab treatment duration	Nivolumab treatment duration of [REDACTED] <sup>a,d</sup>	\$ [REDACTED]	\$ [REDACTED]
SA.7: Pre-progression disease management costs	Equal pre-progression costs in the two treatment arms	\$ [REDACTED]	\$ [REDACTED]
	Nivolumab pre-progression costs 20% less than the comparator arm <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]
SA.3+SA.4	Extrapolation using Weibull model for PFS and OS in both arms + time horizon of 5 years <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]
SA.3+SA.5+SA.7	Extrapolation using Weibull model for PFS and OS in both arms + time horizon of 5 years + equal pre-progression disease management cost between the two arms <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]
<b>Reanalyses using a cost of nivolumab per patient of \$ [REDACTED]*</b>			
Base case	Base case	\$ [REDACTED]	\$ [REDACTED]
SA.3: Method of extrapolation	Log-logistic for nivolumab and Weibull for docetaxel	\$ [REDACTED]	\$ [REDACTED]
	Weibull for both PFS and OS in both arms <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]
SA.4: Time horizon	5 years	\$ [REDACTED]	\$ [REDACTED]
	3 years	\$ [REDACTED]	\$ [REDACTED]
SA.3+SA.5+SA.7	Extrapolation using Weibull model for PFS and OS in both arms + time horizon of 5 years + equal pre-progression disease management cost between the two arms <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]

SA = sensitivity analysis; LY = life year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year

<sup>a</sup> Additional sensitivity analyses performed during the evaluation (or following the Pre-PBAC Response)

<sup>b</sup> The observed utility for progressive disease in the nivolumab arm in CA209-017 was lower than that in the docetaxel arm. The original submission argued that it seemed implausible that patients in the nivolumab treatment arm should have a lower progressive disease utility value. Therefore, the observed utility value for progressive disease in the docetaxel treatment arm was applied to both treatment arms in the base case.

<sup>c</sup> Based on utility value for the progressive disease from Chouaid et al (2013)<sup>4</sup>. When considering erlotinib in March 2014, the PBAC stated that utilities from Chouaid (2013) were more representative estimates (7.03 erlotinib public summary document, March 2014 PBAC meeting).

<sup>d</sup> Arbitrary assumption: one infusion more than the base case ([REDACTED])

\* Cost per patient of nivolumab limited to \$ [REDACTED] as proposed in the Pre-PBAC Response, based on [REDACTED] administrations ([REDACTED] weeks of treatment), assuming that the average patient requires 2 x 100 mg vials and 1 x 40 mg vial of nivolumab.

Source: Table compiled during the evaluation. The base case analysis and the sensitivity analyses were conducted after incorporating the updated Efficient Funding of Chemotherapy fees.

6.38 Results of sensitivity analyses indicated that the model was moderately sensitive to the treatment effect of nivolumab compared with docetaxel in terms of 95%

<sup>4</sup> Chouaid C., Agulnik J., et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. *Journal of Thoracic Oncology*. 2013;8(8):997-1003.

confidence intervals for PFS and OS, the method of extrapolation, the point of extrapolation and the assumption that the pre-progression disease management cost in the nivolumab arm was 40% lower than that in the docetaxel arm.

- 6.39 The time horizon of the economic model was longer than the PBAC recommendation (7.5-year vs 5-year time horizon). Sensitivity analyses also showed that the ICER result would change substantially if the time horizon varied between 1.5 years (around the shortest median time to censoring for PFS and OS in the two treatment arms) and 4 years. Later on, the economic model was less sensitive to the change in time horizon: the ICER would increase by 6% (from \$75,000/QALY - \$105,000/QALY to \$75,000/QALY - \$105,000/QALY) if a time horizon of 5 years was used, compared with a 7.5-year time horizon in the base case.
- 6.40 Multivariate sensitivity analyses conducted during the evaluation suggested that, when assuming a 5-year time horizon and extrapolating PFS and OS using Weibull model for both arms, the ICER increased to \$105,000/QALY - \$200,000/QALY. If equal pre-progression disease management cost between the nivolumab and docetaxel arms was also applied to the model, the ICER would increase further to \$105,000/QALY - \$200,000/QALY. The ESC considered that the true ICER likely sat in the range between \$105,000/QALY - \$200,000/QALY (Weibull for both PFS and OS in both arms) and \$105,000/QALY - \$200,000/QALY (SA.3+SA.5+SA.7).

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

- 6.41 The total drug cost per patient was \$ [REDACTED]. This was calculated using the proposed effective dispensed price, assuming an average patient body weight of 75.2 kg, requiring 225.6 mg of nivolumab. The dose was assumed to be supplied from 2 x 100 mg vials and 1 x 40 mg vial of nivolumab (allowing for wastage), with an average of [REDACTED] infusions per patient, as observed from CA209-017 (without any extrapolation over time). It was also assumed that 15% of the drug would be dispensed in public hospitals and 85% in private hospitals.
- 6.42 This was compared with a total cost of \$ [REDACTED] for treatment with docetaxel, based on its usage in CA209-017.

**Estimated PBS usage & financial implications**

- 6.43 This re-submission was not considered by DUSC.
- 6.44 As for the original submission, the re-submission used an incidence-based approach to estimate the eligible population. This was appropriate.
- 6.45 The main differences between the re-submission and the original submission were:
- The proportion of patients diagnosed with NSCLC who were assumed to have squamous histology was increased from 18.3% to 25.8%, as recommended by DUSC;
  - The proposed effective price for nivolumab was reduced;
  - The mean number of nivolumab infusions per patient was increased from [REDACTED] infusions to [REDACTED] infusions, in line with updated data from trial CA209-017; and
  - Drug wastage was included.

- 6.46 The re-submission's estimates for the proportion of patients receiving each treatment option were the same as those in the original submission. The assumptions in the treatment algorithms were based on advice from the eight expert members of the sponsor's advisory board. The level of agreement among these advisors was not reported, nor was any justification provided for the proportions proposed. Consequently, there was substantial uncertainty in the estimated number of patients likely to be treated.
- 6.47 The DUSC considered that the number of eligible patients receiving prior platinum-based chemotherapy was likely to be underestimated by assuming a relatively large proportion (25%) receive single agent chemotherapy instead. There would be an incentive to use doublet chemotherapy over single agents in order to access nivolumab (paragraph 6.42, 5.06 nivolumab PSD, March 2016 PBAC Meeting).
- 6.48 The average cost of nivolumab per patient was likely to be underestimated, as the duration of nivolumab treatment in practice may be longer than the mean treatment duration observed from the 2-year minimum follow-up data in CA209-017, given that 8% of patients in the trial were still receiving nivolumab.
- 6.49 The PBAC previously noted the DUSC's concerns about the potential for use of nivolumab beyond the restriction (paragraph 7.10, 5.06 nivolumab PSD, March 2016 PBAC Meeting). These concerns included potential use in earlier lines of therapy, use in patients with a performance status that is worse than those participating in the key trial (i.e. ECOG<sup>5</sup>>1), and use beyond disease progression (paragraph 6.42, 5.06 nivolumab PSD, March 2016 PBAC Meeting). The proposed restriction was amended in the re-submission to limit eligibility to patients with a performance score of 0 or 1.

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<sup>5</sup> ECOG = Eastern Cooperative Oncology Group performance status

**Table 9: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated	█	█	█	█	█
Number treated – March 2016	█	█	█	█	█
Number of vials <sup>a</sup>					
100mg/10mL	█	█	█	█	█
40mg/4mL	█	█	█	█	█
Number of vials March 2016 <sup>b</sup>					
100mg/10mL	█	█	█	█	█
40mg/4mL	█	█	█	█	█
<b>Estimated net cost to PBS/MBS</b>					
Net cost to PBS <sup>c</sup>	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS March 2016 <sup>d</sup>	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS (at 85% benefit)	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS March 2016 (at 85% benefit)	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Estimated total net cost</b>					
<b>Net cost PBS/MBS</b>	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost PBS/MBS March 2016	\$ █	\$ █	\$ █	\$ █	\$ █

<sup>a</sup> Assuming █ administrations per patient

<sup>b</sup> Assuming █ administrations per patient

<sup>c</sup> Assuming an average body weight of 75.20 kg, each patient, on average, needs 226 mg of nivolumab. To supply 226 mg of nivolumab, the re-submission assumed that 2 × 100 mg/10 mL vials and 1 × 40 mg/4 mL vials were required.

<sup>d</sup> Assuming an average body weight of 74.25 kg, each patient, on average, needs 223 mg of nivolumab. To supply 223 mg of nivolumab, the March 2016 submission assumed 2 × 100 mg/10 mL vials and 0.58 × 40 mg/4 mL vials were required.

Note: Dispensed drug costs in the re-submission estimates have been updated during the evaluation to include the indexation of fees that occurred on 1 July 2016. Patient co-payments have also been updated to \$38.30 general and \$6.20 concessional.

Source: Compiled during the evaluation

The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to PBS would be \$30 - \$60 million.

6.50 The financial estimates presented in the re-submission may be underestimated, given the following:

- In the scenario in which nivolumab was available on the PBS, the number of patients receiving prior platinum-based chemotherapy was likely to be underestimated, as there would be an incentive to use doublet chemotherapy over single agents in order to access nivolumab.
- The average cost per patient for nivolumab may be underestimated as the mean duration of nivolumab treatment in practice may be longer than that observed in trial CA209-017.
- There is potential for use of nivolumab beyond the restriction.

### **Financial Management – Risk Sharing Arrangements**

6.51 The re-submission proposed a revised Special Pricing Arrangement where the published price would be greater than the effective price. The re-submission also indicated that the sponsor would commit to negotiations to manage residual uncertainty with respect to expenditure. The proposed effective price in the re-submission represented an █% reduction compared with the proposed effective price in the original submission.

- 6.52 The Pre-PBAC Response (p.1) proposed an RSA in which the calculation of the annual expenditure caps limits the cost of nivolumab per patient to that resulting from ■ administrations.

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

## **7 PBAC Outcome**

- 7.1 The PBAC deferred its decision on the listing of nivolumab for the treatment of squamous NSCLC as there were concerns regarding the variation in the extent of effectiveness in patients over 75 years, especially given the high ICER presented in the resubmission and doubts about the ability of the proposed RSA to achieve the sponsor's intended effect on this ICER. The PBAC requested that the Department hold discussions with the sponsor in order to develop a proposal for a Managed Entry Scheme (MES) to address these concerns.
- 7.2 The PBAC reiterated its view that there is a high clinical need for new treatments for patients with squamous NSCLC. The PBAC noted, as previously, that the resubmission requested a second-line PBS listing for nivolumab, following progression on or after platinum-based chemotherapy.
- 7.3 The PBAC noted that the revised restriction provided in the resubmission and further clarification in the PSCR appropriately addressed the Committee's previous concerns with regard to performance status and the requirement for stable or responding disease in the continuing restriction. The PBAC also considered it appropriate to include the initiation criterion excluding patients who have received prior therapy with a PD-1 inhibitor.
- 7.4 As previously, the PBAC considered that the nominated comparator, docetaxel, was appropriate.
- 7.5 As previously, the PBAC considered the claim of superior comparative effectiveness and safety over docetaxel to be reasonable.
- 7.6 The PBAC was concerned about the variation in the extent of effectiveness of nivolumab in patients over 75 years of age, with the pre-specified subgroup analyses of CA209-017 suggesting that nivolumab may possibly be inferior to docetaxel in patients aged over 75 years (unstratified HR 1.85, 95% CI: 0.76, 4.51), and noting the abstract of an analysis (Landre et al, J Clin Oncol 34, 2016 (suppl; abstr 3070)<sup>6</sup>) which indicated that the survival benefit of nivolumab in patients older than 75 years appears uncertain. The PBAC considered that it was plausible that nivolumab, and other immunotherapies relying on stimulating an immune response, may prove to be less effective in older patients whose immune systems may no longer be able to respond to such a stimulus. The PBAC considered this likely reduced effectiveness in patients over 75 years of age to be a significant issue given that a large proportion of patients in Australian clinical practice would belong to this age group, with over 50% of patients over the age of 70 at diagnosis (and also noting the National Institute for Health and Care Excellence (NICE) appraisal of nivolumab for squamous NSCLC,

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<sup>6</sup> <http://meetinglibrary.asco.org/content/169457-176>

which quoted the median age at diagnosis of 74 years in England and Wales<sup>7</sup>).

- 7.7 The PBAC maintained its previous view that no clear predictive effect of PD-L1 expression status on the comparative effectiveness of nivolumab was demonstrated in CA209-017. However, the PBAC noted that a range of predictive biomarkers were currently under development and encouraged the sponsor to submit data on these biomarkers should they subsequently prove useful for determining patient selection for treatment with immunotherapy.
- 7.8 The PBAC considered that the incremental cost per QALY gained for nivolumab over docetaxel presented in the resubmission's base case was very high (\$75,000/QALY - \$105,000/QALY), and noted that, although the resubmission had modified aspects of the model inputs, there was residual disagreement about a number of assumptions favourable to nivolumab as raised by the ESC, in particular the method of extrapolation and time horizon. The PBAC considered that these optimistic assumptions in the economic model base case were likely to produce an underestimate of the true ICER. However, in the context of high clinical need, the PBAC advised that the reduced, although still high ICER (\$45,000/QALY - \$75,000/QALY) proposed in the Pre-PBAC Response with a risk share arrangement (RSA) would be in an acceptable range, should the Committee's concerns regarding the likely variation in the effectiveness of nivolumab with regards to age be adequately mitigated through a MES proposal developed between the Department and the sponsor (see further detail below). The PBAC foreshadowed that, if an adequate MES could be developed, this would provide earlier access to eligible patients for whom there is a high clinical need whilst the Committee's concerns about variation in the effectiveness of nivolumab are addressed.
- 7.9 The PBAC also advised that a prerequisite for any recommendation for PBS listing involving the RSA proposal as presented in the Pre-PBAC Response would be sufficient reassurance that this would actually achieve the ICER of \$45,000/QALY - \$75,000/QALY vs. docetaxel as claimed. The PBAC noted that, in addition to the cost per patient, each annual expenditure cap in an RSA also relies on less certain estimates such as numbers of eligible patients and uptake rates. In addition, there would be lags in achieving the estimated number of patients for each year, and in these eligible patients reaching the proposed limit of ■ administrations, both of which would affect how the RSA would relate to the cost per patient for nivolumab contributing to the ICER. The PBAC therefore requested that these matters also be discussed between the Department and the sponsor, and addressed for PBAC reconsideration alongside the fuller MES proposal as outlined below.
- 7.10 The PBAC considered that the financial implications presented in the resubmission may be underestimated due to potential leakage beyond the restriction and uncertainty around treatment duration, however considered that an RSA providing an overall cap based on patient numbers as well as the numbers of doses per patient would offer some certainty of the overall costs to the PBS.
- 7.11 Noting that there are numerous ongoing trials for nivolumab across a range of diseases, the PBAC also encouraged the Department and sponsor to engage in discussions regarding the potential for an RSA across all PBS restrictions.

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<sup>7</sup> <https://www.nice.org.uk/guidance/GID-TAG506/documents/committee-papers>

- 7.12 The PBAC considered that a MES for nivolumab in NSCLC should be based on the following approach:
- should the future data confirm that, for patients aged 75 years or more, there is no significant benefit of nivolumab over appropriate comparators, then the sponsor would rebate the Commonwealth for PBS-dispensed costs of nivolumab over the appropriate comparators for those patients with NSCLC aged 75 years or more
  - should the future data confirm treatment effect variation by biomarker status (such as PD-L1), the sponsor would be required to provide either a submission to justify continued treatment in a broad population regardless of biomarker status or a co-dependent submission proposing eligibility for PBS subsidy be partly determined by a patient's biomarker status. Evaluation of the biomarker would require a co-dependent submission, and thus would also require MSAC consideration.
- 7.13 The PBAC suggested that the Department and the sponsor liaise about the approach to be taken to generate evidence during the proposed MES to be returned as a fuller MES proposal from the sponsor for PBAC consideration. To facilitate this liaison, the PBAC offered the following initial views:
- The initial focus should be a meta-analysis across comparative trials of nivolumab in NSCLC, with consideration also given to conducting a meta-analysis based on individual patient data in addition to data aggregation at the trial level
  - As this initial trial-level meta-analysis may still be underpowered, it should then be expanded to include comparative trials of other existing and emerging immunotherapies with the same or similar mechanism of action on the programmed cell death (PD) pathway
  - Consideration should be given to a second expansion of the meta-analysis to include comparative trials across other cancer types.
- 7.14 This 3-step approach in the MES should be developed as two components in parallel, with separate comparisons of patients (a) aged above and below 75 years, and (b) with and without a predictive biomarker. The fuller MES proposal should outline prospectively how the meta-analyses would be presented, for example outlining the basis for deciding whether the initial focus provides a sufficiently confident conclusion, such that the expanded meta-analyses need not be presented.
- 7.15 Consideration should be given to having the fuller MES proposal include a prospective definition of the comparative trials to be included in each set of meta-analyses, based on the expected availability of their results and with the aim of concluding the MES in a reasonably short period of time. The expected timelines of the MES should then be summarised, together with a rationale for why any potentially suitable comparative trial might be excluded, noting also that it might be possible to complete the meta-analyses for one uncertainty before the other.
- 7.16 The PBAC noted that the fuller MES proposal would need to show how the number of patients aged 75 years or over subsidised via the PBS would be recorded, together with the number of prescriptions dispensed to these patients in order to indisputably calculate the amount of any rebate that might be required at the completion of this component of the MES. If a significantly reduced effectiveness is

demonstrated compared to the appropriate comparators, consideration will then also need to be given as to whether the restriction is tightened with reference to age, or the restriction remain unchanged and the rebating system introduced, or some other transitional arrangement.

**Outcome:**

Deferred

**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 is committed to working with the PBAC to ensure the earliest possible PBS listing of nivolumab for all eligible NSCLC patients, who have progressed on or after platinum based chemotherapy.