

**5.07 NIVOLUMAB, 40 MG/4 ML VIAL, 100 MG/10 ML VIAL,  
OPDIVO<sup>®</sup>, BRISTOL-MYERS SQUIBB AUSTRALIA PTY LTD.**

**1 Purpose of Application**

- 1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC). The PBAC also considered a concurrent submission to list nivolumab for squamous NSCLC.

**2 Requested listing**

- 2.1 The requested restriction 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.

Public Summary Document – March 2016 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Amt	Number of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
NIVOLUMAB			Published Price	
40 mg/4 mL injection 1 × 4 mL vial			\$ [REDACTED] (Private hospitals) <sup>a</sup>	Opdivo®
	360 mg	5	\$ [REDACTED] (Public Hospitals) <sup>a</sup>	Bristol-Myers
100 mg/10 mL injection 1 × 10 mL vial			Effective Price	Squibb Australia
			\$ [REDACTED] (Private hospitals) <sup>a</sup>	Pty Ltd (BQ)
			\$ [REDACTED] (Public hospitals) <sup>a</sup>	

<sup>a</sup> The dispensed prices for the maximum amount of 360 mg have been calculated during the evaluation using the updated remuneration arrangements (from 1 July 2015)<sup>a</sup>. The submission proposed a special pricing arrangement.

<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>Non-squamous</del> non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Locally advanced or metastatic <del>non-squamous</del> non-small cell lung cancer (NSCLC)
<b>Treatment phase:</b>	Initial treatment
<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>	<i>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC</i>  <i>AND</i>  <i>Patient must have a WHO performance status of 1 or less</i>  <i>AND</i>  <i>The treatment must be the sole PBS-subsidised therapy for this condition</i>  <i>AND</i>  <i>The condition must have progressed on or after prior platinum based chemotherapy.</i>
<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>	No increase in the maximum number of repeats may be authorised.  Special Pricing Arrangements apply.

<sup>a</sup> Preparation fee of \$102.67 has been used

<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>Non-squamous</del> non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Locally advanced or metastatic <del>non-squamous</del> non-small cell lung cancer (NSCLC)
<b>Treatment phase:</b>	Continuing treatment
<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>	Patient must have previously been issued with an authority prescription for this drug <i>for this condition</i>  AND  The treatment must be the sole PBS-subsidised therapy for this condition  AND  Patient must be deriving clinical benefit and tolerating treatment.
<b>Prescriber Instructions:</b>	<del>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.</del>
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised.  Special Pricing Arrangements apply.

- 2.2 The submission sought listing on the basis of a cost effectiveness analysis via a direct comparison with the main comparator, docetaxel. An indirect comparison with the minor comparator, pemetrexed, was also presented. No cost-effectiveness analysis was conducted versus pemetrexed, but the submission noted that pemetrexed was listed on the basis of non-inferiority to docetaxel.
- 2.3 The requested restriction did not indicate the role of PD-L1 expression in patient eligibility for nivolumab. The presented evidence indicated there was significant treatment effect variation, with no meaningful overall survival (OS) benefit associated with nivolumab over docetaxel in PD-L1 negative patients, and significant OS benefit in PD-L1 positive patients (see comparative effectiveness below). The ESC advised that nivolumab should be restricted to patients with a positive PD-L1 status.
- 2.4 The requested restriction does not specify performance status, although the key trial only included patients with a performance status of 0 or 1.
- 2.5 The requested restriction did not refer to the inclusion or exclusion of the “not otherwise specified” (NOS) type NSCLC. NOS type NSCLC is included in the current

restrictions for tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, in NSCLC patients. The Pre-Sub-Committee Response (PSCR) (p.3) clarified that it was the sponsor's intention for patients with NOS NSCLC to be eligible for nivolumab under the non-squamous indication. The ESC considered that PD-L1 positive status should be used to define the eligible population, rather than a restriction based on whether the NSCLC is squamous, non-squamous, or not otherwise specified. The ESC advised that this would involve determining an appropriate threshold of PD-L1 expression and a co-dependent consideration of PD-L1 testing involving the Medical Services Advisory Committee (MSAC). The ESC noted that MSAC Application 1414 will request MBS listing of PD-L1 expression testing in the context of pembrolizumab in NSCLC.

- 2.6 The continuation criteria specified that "patient must be deriving clinical benefit and tolerating treatment". This is consistent with the nivolumab draft Product Information (PI), however the recently approved Food and Drug Administration (FDA) prescribing information (9 October 2015) specifies that nivolumab treatment be continued until disease progression or unacceptable toxicity. In the key CA209-057 trial, 25% of nivolumab-treated patients were allowed to continue treatment beyond RECIST defined progression (progression in docetaxel-treated patients was based only on RECIST criteria) until further progression based on a 10% increase in tumour burden volume. The rationale for treatment beyond RECIST defined progression was that immunotherapeutic agents can cause treatment-induced inflammatory responses in tumours which can be mistaken for progression. The PSCR (p.2) stated that the sponsor contacted three clinicians and asked for their interpretation of "deriving clinical benefit". The clinicians agreed that "they would cease treatment if there is radiological progression AND the patient has a worsening of cancer related symptoms AND worsening of performance score." The ESC suggested that the continuing restriction include a criterion that "Patient must not have progressive disease" and a note that "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."

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

### **3 Background**

- 3.1 The submission was made under the TGA/PBAC Parallel Process. Nivolumab was submitted to the TGA for evaluation on 7 January 2015. The dossier included trial data in melanoma, squamous and non-squamous NSCLC. The proposed TGA indication, relevant for the current submission, is for the treatment of locally advanced or metastatic non-squamous NSCLC, with progression on or after prior chemotherapy. According to the TGA delegate's overview dated 5 January 2016 seeking the advice of the 5 February 2016 ACPM meeting, a registration decision for non-squamous NSCLC was still pending although the delegate:
- proposed the following indication for nivolumab: As monotherapy for the treatment of locally advanced or metastatic non-squamous NSCLC in patients with progression on or after chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, nivolumab should be used after progression on or after targeted therapy; and

- noted that there is no currently registered PD-L1 assay in Australia.
- 3.2 This was the first consideration of nivolumab by the PBAC for NSCLC. A previous submission to list nivolumab monotherapy for Stage III/IV melanoma was rejected by the PBAC in July 2015 and subsequently recommended by the PBAC in November 2015. A submission for nivolumab in combination with ipilimumab (also for Stage III/IV melanoma) was rejected by the PBAC in November 2015. Another PD-1 inhibitor, pembrolizumab, was recommended for melanoma by the PBAC in March 2015.

#### **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. Approximately 20% of patients will receive TKIs first-line (targeting epidermal growth factor receptor (EGFR) gene mutations or anaplastic lymphoma kinase (ALK) translocations), followed by platinum-based chemotherapy upon progression, and subsequent pemetrexed or docetaxel. Patients with no EGFR mutations/translocations would initiate treatment with platinum-based chemotherapy, and subsequent pemetrexed or docetaxel.
- 4.2 The intended listing was for patients who have failed platinum-based chemotherapy, thus displacing pemetrexed or docetaxel further down the treatment pathway. The proposed mechanism of action of nivolumab was that it blocks programmed cell death-1 (PD-1) inhibition of the immune system preventing ligand binding. However, the submission did not propose restricting the listing of nivolumab to patients with non-squamous NSCLC tumours that express PD-L1 (PD-L1 positive). The submission argued that PD-L1 expression is likely not an appropriate immune marker, interpretation of PD-L1 expression testing varies, and all patients in the key trial (CA209-057) benefited from nivolumab treatment over docetaxel regardless of PD-L1 status. The ESC proposed that nivolumab should be restricted to patients with a positive PD-L1 status. The Pre-PBAC Response (p.1) disagreed that PBS-listed nivolumab should be restricted to patients who are PD-L1 expression positive, and claimed that this would be misaligned with treatment guidelines and inconsistent with study conclusions from the key clinical trial. The ESC further noted that, in patients with tumour EGFR mutations or ALK genomic aberrations, although the proposed TGA indication is for nivolumab to be used after progression on or after targeted therapy, the sponsor's advisory board considered that this group of patients were less likely to derive clinical benefit from nivolumab.

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

## **5 Comparator**

- 5.1 The submission nominated docetaxel as the main comparator and pemetrexed as a minor comparator. The submission argued that the majority of patients use pemetrexed as maintenance therapy with platinum-based chemotherapy and thus would likely be treated with docetaxel upon progression. The ESC considered that both docetaxel and pemetrexed are relevant comparators. Pemetrexed is used as maintenance therapy in practice, but the extent of such use and its cost-effectiveness is unknown (Public Summary Documents for gefitinib and erlotinib, PBAC Consideration: July 2013).

*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 for the sponsor discussed how the drug would be used in practice, and addressed other matters in response to the Committee's questions about obtaining tissue for PD-L1 expression testing, what level of performance status would be suitable for nivolumab treatment, the likely role of nivolumab as monotherapy, sequential therapy or combination therapy, the predictive value of PD-L1 expression status for NSCLC compared to its likely role in other cancers, and the likelihood of using nivolumab as first-line in NSCLC.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The comment from the Lung Foundation emphasised that effective, safe and well tolerated treatments for lung cancer in Australia remain limited, and supported early access to treatment where evidence shows benefit. A comment from Merck Sharp and Dohme discussed the importance of PD-L1 testing and how the effectiveness of PD-L1 therapies correlates with levels of expression of PD-L1.

### ***Clinical trials***

- 6.3 The submission was based on one open-label head-to-head randomised controlled trial (CA209-057: N=582) comparing nivolumab with docetaxel in previously treated patients with metastatic non-squamous NSCLC. An indirect comparison with pemetrexed using docetaxel as the common reference was also conducted based on CA209-057 and a retrospective non-squamous subgroup analysis (Scagliotti (2009: N=399) of a trial which compared pemetrexed with docetaxel in NSCLC (Hanna et al (2004): N=571). The direct comparison with docetaxel formed the main basis of the submission. No cost-effectiveness analysis was conducted versus pemetrexed.

6.4 Details of the trial presented in the submission are provided in Table 1.

**Table 1: Trial and associated reports presented in the submission to support the main clinical claim**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
CA209-057	Primary clinical study report CA209057 - An open-label randomized phase III trial of BMS-936558 (nivolumab) versus docetaxel in previously treated metastatic non-squamous non-small cell lung cancer (NSCLC), (database lock March 2015).  <u>Publication</u> Borghaei H, Paz-Ares, L. Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer.  <u>Abstract</u> Horn et al (2015) 30th ESMO European Cancer Congress (updated overall survival, database lock July 2015).	May 2015  <i>New England Journal of Medicine</i> 2015; 373:1627-39  <i>European Cancer Congress</i> ; Vienna, Austria, September 25-29, 2015.

Source: Table 10, Section B.2 of the submission.

6.5 The key features of the direct randomised trial are summarised in Table 2.

**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 75 mg/m<sup>2</sup> Q3W</b>						
CA209-057	582	R, OL Database lock March 2015 (follow-up 13.2 months) and database lock July 2015 (most updated: follow-up 17.1 months)	Low for OS High for AEs and QoL.	Patients (unselected for PD-L1 status) who had failed platinum-based chemotherapy	Overall survival	Used

Q2W=every 2 weeks; Q3W=every 3 weeks; OL=open label; OS=overall survival; R=randomised; AEs=adverse events; QoL=quality of life

Source: compiled during the evaluation.

6.6 There was no confounding of OS by treatment switching at the first database lock (March 2015) and minimal confounding of OS at the second database lock (July 2015). Randomisation was fairly successful as the balance of baseline characteristics across treatment arms was reasonable. The open-label design of the trial may have affected reported incidence and severity of immune-related adverse events (AEs) and patient responses to quality of life questionnaires.

### **Comparative effectiveness**

#### Direct comparison with docetaxel

6.7 Table 3 summarises the OS results from database lock March 2015 and database lock July 2015 from CA209-057. Figures 1-2 present the Kaplan-Meier curves for the different follow-up periods.

**Table 3: CA209-057 - Overall survival results (Intention-to-treat: Unselected by PD-L1 status)**

	CA209-057 CSR Database Lock March 2015 (13.2 months minimum follow-up)		Borghaei et al (2015) <sup>a</sup> Database Lock July 2015 (17.1 months minimum follow-up)	
	Nivolumab N=292	Docetaxel N=290	Nivolumab N=292	Docetaxel N=290
Number of events, n (%)	190 (65.1)	223 (76.9)	206 (70.5)	236 (80.8)
Median(months) (95% CI)	12.2 (9.7, 15.0)	9.4 (8.1, 10.7)	12.2 (9.7, 15.1)	9.4 (8.1, 10.7)
Difference (nivolumab minus docetaxel)	2.8 months		2.8 months	
Kaplan-Meier OS rate, % surviving at time point (95% CI)	At 12 months		At 18 months	
	50.5 (44.6, 56.1)	39 (33.3, 44.6)	39 (34.0, 45.0)	23 (19.0, 28.0)
<b>Nivolumab versus docetaxel</b> Stratified HR; stratified log-rank: p-value	0.73 (95.92%CI: 0.59, 0.89) <sup>b</sup> ; p=0.0015		0.72 (95%CI: 0.60, 0.88) <sup>b</sup> ; p = 0.0009	

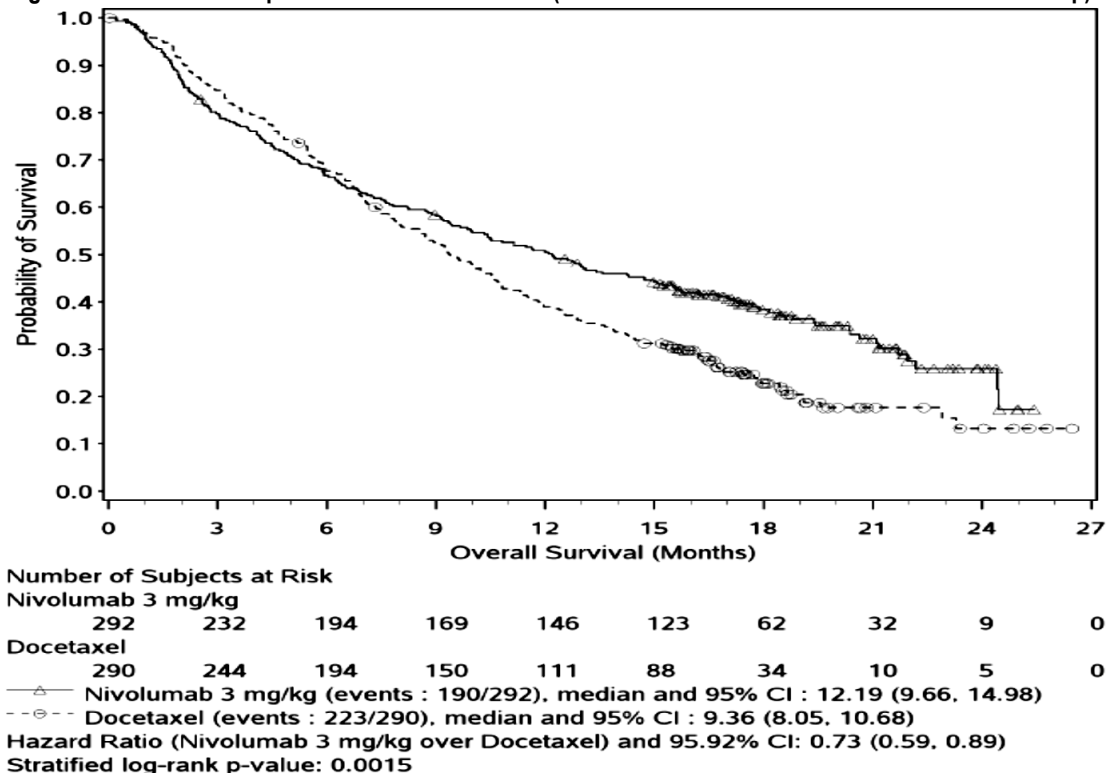
CI=confidence interval; HR=hazard ratio; CSR=clinical study report; NR=not reported

<sup>a</sup> Publication by Borghaei et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *New England Journal of Medicine* 2015; 373:1627-39.

<sup>b</sup> Proportional hazards assumption was not met. 95.92% confidence intervals are reflective of the adjustment for interim analysis.

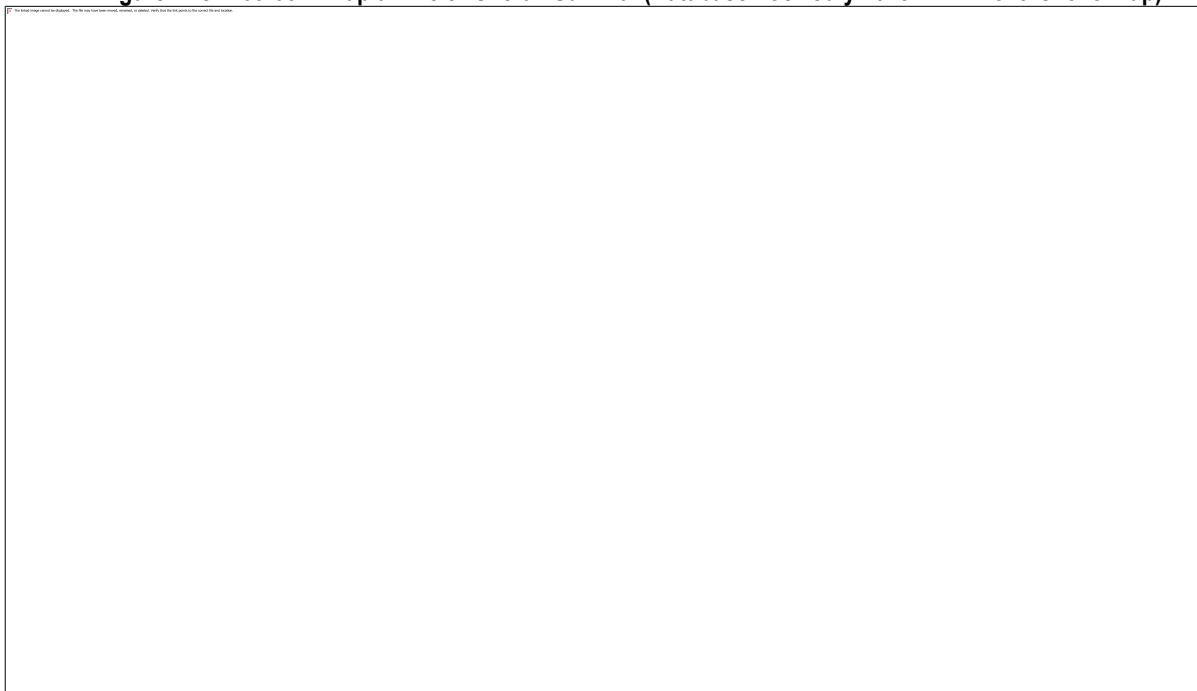
Source: Table 25, Section B.6.1 of the submission.

**Figure 1: CA209-057 - Kaplan-Meier Overall Survival (Database Lock March 2015: 13.2 months follow-up)**



Source: Figure 9, Section B.6.1 of the submission.

Figure 2: CA209-057 - Kaplan-Meier Overall Survival (Database Lock July 2015: 17.1 months follow-up)



Source: Source: Figure 10, Section B.6.1 of the submission.

- 6.8 Intention-to-treat analysis: The results were similar for both follow-up periods and indicated a difference of approximately 3 months in median OS and a statistically significant 28% reduction in risk of death favouring nivolumab over docetaxel. From the updated database lock July 2015 with 17.1 month minimum follow-up analysis, the OS rate at 18 months was 39% (95%CI, 34%, 45%) in the nivolumab treatment arm compared with 23% (95%CI 19%, 28%) in the docetaxel treatment arm. Interpretation of these results was hindered by the apparent non-constant relative hazard over time. Statistical tests demonstrated that the proportional hazards assumption was not met and this is consistent with the visual observation of the Kaplan-Meier curves. The survival curves crossed with an initial increase and a subsequent decrease in hazard of death associated with nivolumab compared with docetaxel. The observed change in relative hazards over time might have been due to the biological action of the drug or also possibly to differentially responsive sub-populations. Thus the estimated HR, as a measure of the relative treatment effect or reduction in risk, was misleading given the measure's dependency on follow-up time. Alternatively, one could rely on the log rank test and restricted mean survival times (Royston (2013))<sup>b</sup>. Restricted means were not provided in the submission. The log-rank p-values were statistically significant favouring nivolumab in both the original and updated analyses. The PSCR (p.6) provided Kaplan-Meier OS curves from a sensitivity analysis of all randomised subjects alive at month 3, showing separation of curves, improved hazard ratios, and larger median OS differences favouring nivolumab.

#### Treatment effect variation of nivolumab by PD-L1 status

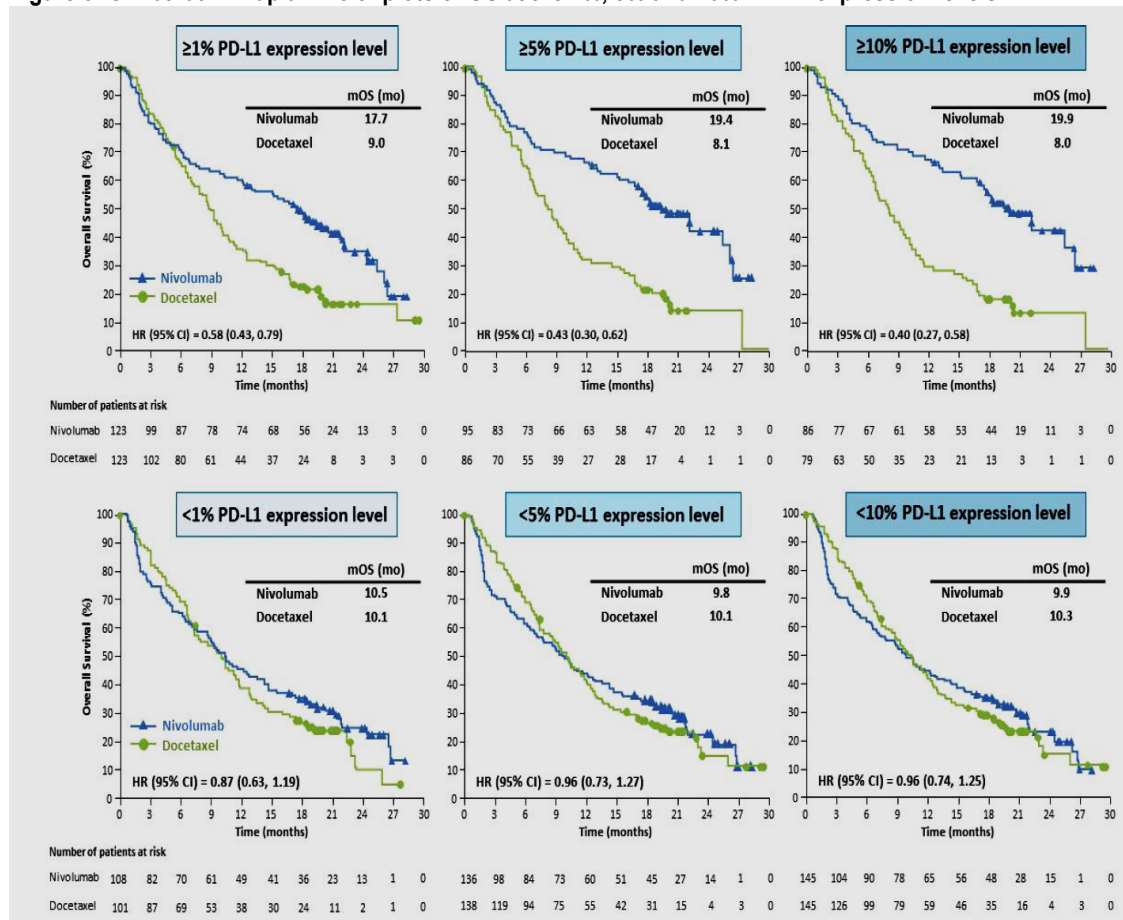
<sup>b</sup> Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Medical Research Methodology. 2013;13(1):152.

- 6.9 Analyses of treatment effect variation were conducted on the following PD-L1 expression subsets: <1% vs. ≥1%, <5% vs. ≥5%, and <10% vs. ≥10%. Analyses based on mutually exclusive expression subsets, such as <1% vs. ≥1% to <5% vs. ≥5% to <10% vs. ≥10%, would have been more informative.
- 6.10 The submission did not request testing for PD-L1 positivity as an eligibility criterion for nivolumab. The argument presented in the submission was that all patients benefited from nivolumab treatment over docetaxel regardless of PD-L1 status with at least a superior safety profile. The Protocol Advisory Sub-Committee of the Medical Services Advisory Committee (MSAC) has recently considered a Protocol requesting a Medicare Benefits Schedule (MBS) listing for testing of PD-L1 expression in advanced NSCLC in the context of pembrolizumab (another PD-1 inhibitor)<sup>c</sup>.
- 6.11 The OS HR from the CA209-057 ITT analysis (unselected for PD-L1 positivity) was difficult to interpret due to a breach of the proportional hazards assumption.
- 6.12 The Kaplan-Meier OS curves, by PD-L1 status, are presented in Figure 3 (updated July 2015 database lock). PD-L1 status was balanced across the nivolumab and docetaxel treatment arms. Median OS times were similar between nivolumab and docetaxel (approximately 10 months) in patients with PD-L1 negative expression levels (<1%, <5% and <10%). In contrast, in patients with PD-L1 positive expression levels patients (≥1%, ≥5%, and ≥10%), nivolumab was associated with median OS times almost twice those observed for docetaxel (18-20 months vs. 8-9 months). In the PD-L1 negative populations, the Kaplan-Meier curves similarly crossed over. It would therefore be incorrect and misleading to interpret the non-statistically significant HRs observed in the negative PD-L1 expression populations (for example in <5% PD-L1 patients: 0.96 (95% CI: 0.73, 1.27)) as indicative of a lack of meaningful difference. Such an interpretation ignores the possibility that some patients may be experiencing harm with nivolumab.

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<sup>c</sup> This listing is required should the sponsor decide to lodge an integrated co-dependent submission for use of PD-L1 testing to determine eligibility for pembrolizumab (Consultation Protocol 1414 available at [www.msac.gov.au](http://www.msac.gov.au)).

Figure 3: CA209-057 - Kaplan-Meier plots of OS at the 1%, 5% and 10% PD-L1 expression levels

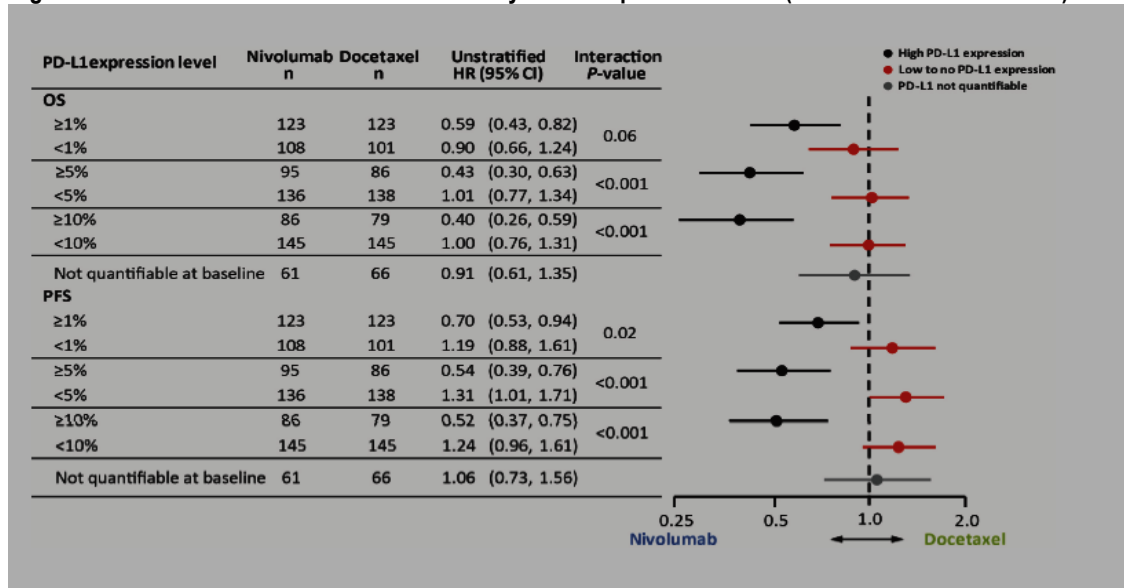


CI=confidence interval; HR=hazard ratio; mo=months; mOS=median overall survival; PD-L1=programmed-cell death ligand-1.

Source: Figure S.8B, Appendix to publication by Borghaei et al. Nivolumab versus Docetaxel in Advanced Non-squamous Non-Small-Cell Lung Cancer. *New England Journal of Medicine* 2015; 373:1627-39.

- 6.13 Figure 4 indicates a clear treatment effect variation with the majority of the tests for interaction statistically significant for both OS and progression-free survival (PFS).

Figure 4: CA209-057 - Plot of OS and PFS HRs by PD-L1 expression levels (March 2015 database lock)



Interaction p-values from Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction.

CI=confidence interval; HR=hazard ratio; OS=overall survival; PD-L1=programmed-cell death ligand-1; PFS=progression-free survival

Source: Figure S.7, Appendix to publication by Borghaei et al. Nivolumab versus Docetaxel in Advanced Non-squamous Non-Small-Cell Lung Cancer. New England Journal of Medicine 2015; 373:1627-39.

6.14 “EGFR-mutation status positive” and “Third-line treatment” subgroup analyses: Maintenance therapy (yes/no) and line of therapy (second/third) were stratification variables for randomisation in CA209-057. In the OS analysis, the HR favoured nivolumab over docetaxel in the majority of exploratory subgroup analyses, although the results were not statistically significant. The exceptions to the direction of effect were the following subgroup analyses: 1) “Third line” therapy (N=66, HR=1.34; 95% CI: 0.73, 2.43), 2) “Rest of world” region which included Asia and Australia (N=98, HR=1.49; 95% CI: 0.91, 2.45), and 3) “EGFR mutation status positive” (N=82, HR=1.18; 95% CI: 0.69, 2.00). These subgroup analyses were problematic due to small patient numbers and potential imbalances across treatment arms which could not be assessed due to lack of baseline data by treatment arm. However, a preliminary TGA clinical evaluation report (which became available during the evaluation) concluded there was clear evidence of good efficacy (relative to docetaxel) for nivolumab in non-squamous NSCLC patients who have failed initial platinum-based therapy and whose tumours are PD-L1 positive and whose tumours are not EGFR mutation positive. In other subgroups, the evidence for efficacy was stated to be “less clear-cut”.

### Comparative harms

6.15 The tables below provide a summary of adverse events (AEs) from CA209-057.

6.16 The submission conducted numerous statistical comparisons between nivolumab and docetaxel. It was not apparent from the submission whether there was any adjustment for multiplicity to minimise the risk of a Type I error. Putative statistically significant findings need to be cautiously interpreted when there is no adjustment for

multiple comparisons<sup>d</sup>. There were no statistically significant differences in “any cause” AEs between the nivolumab and docetaxel treatment arms although for drug-related severe (Grade  $\geq 3$ ) AEs and AEs leading to discontinuation, the statistically significant differences favoured nivolumab. Significantly more severe AEs were reported in the docetaxel treatment arm as compared with the nivolumab treatment arm (46% versus 67%), specifically for neutropenia (27% versus 0%) which was considered to be study-drug related. These data need to be interpreted in the context of the open-label design of the CA209-057 trial.

Table 4: CA209-057: Summary of overall adverse events

Treatment arm	Nivo	Doc	RR (95% CI) Nivo vs. Doc	RD (95% CI) Nivo vs. Doc
N	287	268		
<b>One or more AE - n (%)</b>				
Any cause	280 (97.6)	265 (98.9)	0.99 (0.96, 1.01)	-0.01 (-0.04, 0.01)
Study drug related	<b>199 (69.3)</b>	<b>236 (88.1)</b>	<b>0.79 (0.72, 0.86)</b>	<b>-0.19 (-0.25, -0.12)</b>
<b>SAE -n (%)</b>				
Any cause	134 (46.7)	111 (41.4)	1.13 (0.93, 1.36)	0.05 (-0.03, 0.14)
Study drug related	21 (7.3)	15 (5.2)	1.31 (0.69, 2.48)	0.02 (-0.02, 0.06)
<b>Severe AE (Grade <math>\geq 3</math>) n (%)</b>				
Any cause	<b>132 (46.0)</b>	<b>180 (67.2)</b>	<b>0.68 (0.59, 0.80)</b>	<b>-0.21 (-0.29, -0.13)</b>
Study drug related	<b>30 (10.5)</b>	<b>144 (53.7)</b>	<b>0.19 (0.14, 0.28)</b>	<b>-0.43 (-0.50, -0.36)</b>
<b>AE leading to discontinuation - n (%)</b>				
Any cause	48 (16.7)	58 (21.6)	0.77 (0.55, 1.09)	-0.05 (-0.11, 0.02)
Study drug related	<b>14 (4.9)</b>	<b>40 (14.9)</b>	<b>0.33 (0.18, 0.59)</b>	<b>-0.10 (-0.15, -0.05)</b>
Death - n (%)	<b>185 (64.5)</b>	<b>204 (76.1)</b>	<b>0.85 (0.76, 0.94)</b>	<b>-0.12 (-0.19, -0.04)</b>

Statistical significant results bolded.

AE = adverse event; DC = discontinuation; Doc = docetaxel; Nivo = nivolumab; RD = risk difference; RR = relative risk; CI = confidence interval; SAE = serious adverse event.

<sup>a</sup> One death was attributed to nivolumab (encephalitis); association to nivolumab was changed after database lock

Source: Table 31, Section B.6.2 of the submission.

<sup>d</sup> Mehrotra et al (2004). Use of the false discovery rate for evaluating clinical safety data. *Statistical methods in medical research* 2004; 13; pp227-238.

Table 5: CA209-057: Most frequent severe (Grade≥3) adverse events

Treatment arm	Nivo	Doc	RR (95% CI) Nivo vs. Doc	RD (95% CI) Nivo vs. Doc
N	287	268		
<b>Regardless of causality - n (%)</b>				
One or more AE	<b>132 (46.0)</b>	<b>180 (67.2)</b>	<b>0.68 (0.59,0.80)</b>	<b>-0.21 (-0.29, -0.13)</b>
Fatigue	9 (3.1)	18 (6.7)	0.47 (0.21, 1.02)	-0.04 (-0.07, 0.00)
Decreased appetite	5 (1.7)	4 (1.5)	1.17 (0.32, 4.30)	0.00 (-0.02, 0.02)
Cough	1 (0.3)	0	0.00	0.00 (0.00, 0.01)
Constipation	2 (0.7)	2 (0.7)	0.93 (0.13,6.58)	0.00 (-0.01,0.01)
Dyspnoea	14 (4.9)	10 (3.7)	1.31 (0.59,2.89)	0.01 (-0.02,0.05)
Nausea	5 (1.7)	2 (0.7)	2.33 (0.46,11.93)	0.01 (-0.01,0.03)
Asthenia	10 (3.5)	11 (4.1)	0.85 (0.37, 1.97)	-0.01 (-0.04, 0.03)
Diarrhoea	3 (1.0)	3 (1.1)	0.93 (0.19, 4.59)	0.00 (-0.02, 0.02)
Anaemia	5 (1.7)	12 (4.5)	0.39 (0.14,1.09)	-0.03 (-0.06, 0.00)
Neutropenia	<b>1(0.3)</b>	<b>75 (28.0)</b>	<b>0.01 (0.00,0.09)</b>	<b>-0.28 (-0.33, -0.22)</b>
<b>Study drug related - n (%)</b>				
One or more AE	<b>30 (10.5)</b>	<b>144 (53.7)</b>	<b>0.19 (0.14, 0.28)</b>	<b>-0.43 (-0.50, -0.36)</b>
Fatigue	<b>3 (1.0)</b>	<b>13 (4.9)</b>	<b>0.22 (0.06,0.75)</b>	<b>-0.04 (-0.07, -0.01)</b>
Nausea	2 (0.7)	2 (0.7)	0.93 (0.13, 6.58)	0.00 (-0.01, 0.01)
Decreased appetite	0	3 (1.1)	0.00	-0.01 (-0.02, 0.00)
Asthenia	1 (0.3)	6 (2.2)	0.16 (0.02, 1.28)	-0.02 (-0.04, 0.00)
Diarrhoea	2 (0.7)	3 (1.1)	0.62 (0.10, 3.70)	0.00 (-0.02, 0.01)
Anaemia	1(0.3)	7 (2.6)	0.13 (0.02, 1.08)	-0.02 (-0.04, 0.00)
Neutropenia	<b>0</b>	<b>73 (27.2)</b>	<b>0.00</b>	<b>-0.27 (-0.33, -0.22)</b>

Statistical significant results bolded.

AE = adverse event; Doc = docetaxel; Nivo = nivolumab; RD = risk difference; RR = relative risk; CI = confidence interval

Source: Table 33, Section B.6.2 of the submission.

- 6.17 The CSR for the CA209-057 trial presented data on Grade 3-4 “Select AEs” (potentially associated with the use of nivolumab). Statistical comparisons were conducted during the evaluation of the proportion of these AEs. Nivolumab was associated with a significantly higher proportion of Grade 3-4 endocrine AEs compared with docetaxel (27/287 (9.4%) vs. 1/268 (0.4%); RR= 25.12 (95% CI: 6.9, 92.8); RD=9.0% (95% CI: 5.4%, 12.7%) and with a significantly lower proportion of Grade 3-4 gastrointestinal AEs (22/287 (7.7%) vs. 62/268 (23.1%); RR= 0.33 (95% CI: 0.22, 0.51); RD=-15.5% (95% CI: -21.4%, -9.5%).
- 6.18 The ESC noted that the adverse event of fatal encephalitis is linked to nivolumab, and that a TGA condition of registration is provision of the results of the enhanced pharmacovigilance study of immune-related encephalitis, mandated by the FDA.

### Benefits/harms

- 6.19 A summary of the comparative benefits and harms for nivolumab versus docetaxel in an unselected ITT non-squamous NSCLC population is presented in the table below. The OS curves cross for patients receiving the two drugs, making it difficult to interpret the HR as the proportional hazards assumption was not met. Comparative benefits were also presented by PD-L1 status (PD-L1 ≥ 5% vs. PD-L1 < 5%) as the data indicated significant variation in treatment effect. Safety data by PD-L1 status were not presented as the AEs across PD-L1 subsets were not substantially different.

**Table 6: CA209-057: Summary of comparative benefits and harms for nivolumab and docetaxel**

	Nivolumab	Docetaxel	Event rate/100 patients (95% CI)		RD/100 patients (95% CI)	
			Nivolumab	Docetaxel		
<b>ITT-Unselected for PD-L1 status</b>						
<b>Benefits</b>						
Overall survival (OS)						
Kaplan-Meier OS rate <sup>a</sup> at 12 months (Database lock: March 2015)	147/292	113/290	51 (45, 56)	39.0 (33, 45)	12 (3, 19)	
Kaplan-Meier OS rate <sup>a</sup> at 18 months <sup>b</sup> (Database lock: July 2015)	114/292	67/290	39 (34, 45)	23 (19, 28)	16 (8, 23)	
	<b>Nivolumab</b>	<b>Docetaxel</b>	<b>Absolute difference</b>		<b>HR (95% CI)</b>	
Median OS, months (95% CI) <sup>c</sup> (July 2015 Database Lock, 17.1 months minimum follow-up)	12.2 (9.7, 15.0)	9.4 (8.1, 10.7)	2.8		0.72 (0.60, 0.88)	
<b>Harms (Safety set)</b>						
	Nivolumab	Docetaxel	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Nivolumab	Docetaxel	
Drug related severe AEs (Grade ≥3) <sup>d</sup>	30/287	144/268	0.19 (0.14, 0.28)	10.5	53.7	-0.43 (-0.50, -0.36)
Grade ≥3 drug-related neutropenia	0/287	73/268	0.00 (0.00)	0.0	27.2	-0.27 (-0.33, -0.22)
"Select" <sup>e</sup> Grade 3-4 endocrine related AEs	27/287	1/268	25.12 (6.90, 92.80)	9.4	0.4	0.09 (0.05, 0.13)
<b>PD-L1 positive (≥5%)<sup>f</sup></b>						
<b>Benefits<sup>f</sup></b>						
Overall survival (OS)						
	<b>Nivolumab</b>	<b>Docetaxel</b>	<b>Absolute difference</b>		<b>HR (95% CI)</b>	
Median OS, months (95% CI)	19.4 (NR)	8.1 (NR)	11.3		0.43 (0.30, 0.63)	
<b>PD-L1 negative (&lt;5%)<sup>f</sup></b>						
<b>Benefits<sup>f</sup></b>						
Overall survival (OS)						
	<b>Nivolumab</b>	<b>Docetaxel</b>	<b>Absolute difference</b>		<b>HR (95% CI)</b>	
Median OS, months (95% CI)	9.8 (NR)	10.1 (NR)	-0.3		0.96 (0.73, 1.27)	

<sup>a</sup> Numerator calculated from proportions provided and total number of patients randomised to treatment arm.

<sup>b</sup> Data sourced from Horn et al 2015.

<sup>c</sup> Median OS and HRs were similar for both the March 2015 (13.2 months minimum follow up) and July 2015 (17.1 months minimum follow up) database locks. NOTE: Proportional hazards assumption NOT met.

<sup>d</sup> Drug-related serious AEs (SAEs) were similar across treatment arms.

<sup>e</sup> Select AEs were AEs of special interest that were potentially associated with the use of nivolumab (sourced from the CA209-057 clinical study report)

<sup>f</sup> Median OS times for nivolumab arm were also double that for docetaxel for positive PD-L1 ≥ 1% and PD-L1 ≥ 10% subgroups (18 months vs. 9 months and 20 months vs. 8 months, respectively) whereas the median OS was the same for nivolumab and docetaxel for the complement negative PD-L1 < 1% and PD-L1 < 10% subgroups (10.5 months vs. 10 months and 9.9 months vs. 10.3 months, respectively)

AEs=adverse events; RD=risk difference; RR=risk ratio; CI=confidence interval; PD-L1=programmed-cell death ligand-1

Source: Compiled during the evaluation and Table 3 of the Executive Summary of the submission.

- 6.20 On the basis of the direct evidence presented by the submission, for every 100 non-squamous NSCLC patients (unselected for PD-L1 expression) treated with nivolumab in comparison to docetaxel:
- Approximately 16 additional patients would be expected to be alive at 18 months. However, whilst nivolumab doubled median OS compared to docetaxel in PD-L1 positive patients, there was no meaningful median OS difference between nivolumab and docetaxel in PD-L1 negative patients;
  - Approximately 43 fewer patients would experience a drug-related Grade 3 / 4 AE, 27 fewer patients would experience drug-related neutropenia, but an additional 9 patients would experience a Grade 3-4 endocrine AE. These differences would be expected to be fairly similar for both PD-L1 positive and negative patients.

### ***Clinical claim***

- 6.21 The submission described nivolumab as superior in terms of comparative effectiveness and superior in terms of comparative safety over docetaxel for the treatment of Stage III/Stage IV non-squamous NSCLC after progression on or after platinum doublet chemotherapy. Analyses by PD-L1 status indicated that nivolumab was not superior, in terms of OS, to docetaxel in patients who were PD-L1 expression negative. In terms of safety, lower rates of Grade  $\geq 3$  immuno-related AEs were associated with nivolumab compared to docetaxel in CA209-057. Another possible reason for the low frequency of these severe AEs could have been the open-label nature of the trial.
- 6.22 The ESC considered that the submission's claim of superior comparative effectiveness and superior comparative safety over docetaxel was reasonable in patients who are PD-L1 positive.
- 6.23 The PBAC considered that the incremental survival benefit of nivolumab appeared to be limited to patients who were PD-L1 positive, and that the claim of superior comparative effectiveness of nivolumab over docetaxel was strongest in patients who are PD-L1 positive.
- 6.24 The PBAC considered that the claim of superior comparative safety was reasonable, however also noted that nivolumab was associated with a significantly higher proportion of patients with Grade 3 and 4 endocrine adverse events than docetaxel.

### ***Economic analysis***

- 6.25 The economic evaluation was a Markov model with three health states – progression-free, post-progression and death. In the model, patients are treated either by nivolumab or docetaxel and enter the progression-free health state in the first cycle. In the subsequent cycles, patients can remain in the progression-free state, transit to the post-progression state or die. Transition probabilities were not explicitly calculated or used in the model. Instead, the proportion of patients in the progression-free state at each model cycle was obtained directly from patient level progression-free data of the CA209-057 trial and the extrapolated PFS curves. The proportion of patients who died was calculated from the OS data (1-OS) at each model cycle. The proportion of patients in the post-progression state was the difference between those in the OS health state and the PFS state at each time point in the modelled economic evaluation.

**Table 7: Summary of model structure and rationale**

Time horizon	10 years in the model base case versus 18 months in the trial
Outcomes	LYG and QALYs
Methods used to generate results	Three states (progression-free, progressed and death) Markov model. 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

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

6.26 The key drivers of the model are summarised below.

**Table 8: Key drivers of the model**

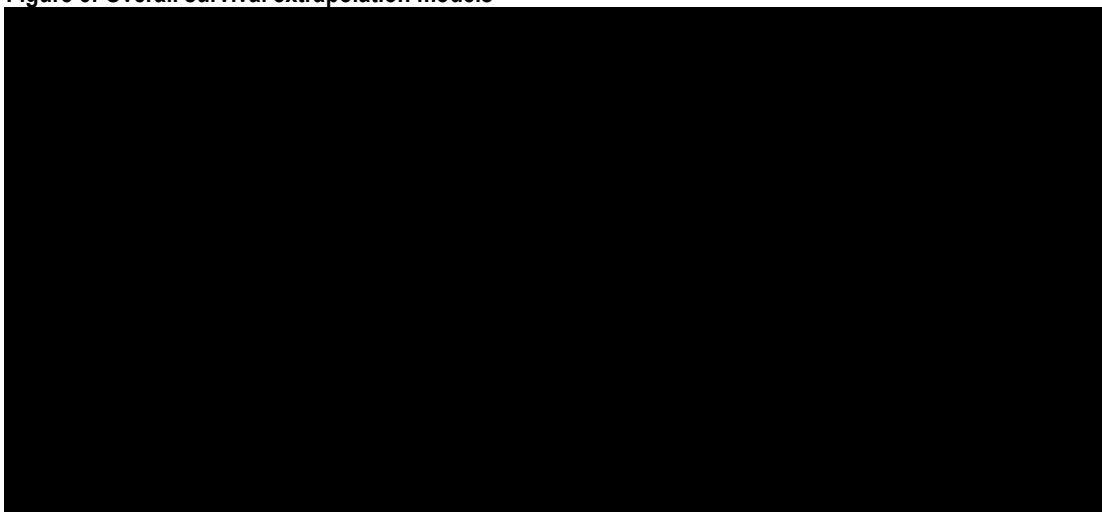
Description	Method/Value	Impact
Time horizon	10 years; assumed from 18 month trial duration	High, favours nivolumab
Method of extrapolation	Log-logistic distribution for PFS and OS in the nivolumab arm, log-logistic distribution for PFS in the docetaxel arm and Weibull distribution for OS in the docetaxel arm, assuming continued treatment effect	High, favours nivolumab
Duration of nivolumab treatment	CA209-057 mean trial-based treatment duration – i.e. truncated with respect to resource use	High, favours nivolumab
Ongoing disease management costs for progressive disease	The costs of ongoing disease management post-progression for years 2-5 and beyond 5 years were assumed to be halved and quartered respectively compared with the costs in the first two years.	High, favours nivolumab
Time point of extrapolation	Median time to follow-up	High, favours nivolumab
Utility value	CA209-057 trial-based utility data	Moderate, favours nivolumab
Ongoing disease management costs for pre-progression disease	The submission assumed that during the pre-progression period, patients treated with nivolumab would require 80% of the disease management costs of those treated with docetaxel, based on one clinician's opinion.	Low, favours nivolumab

PFS=progression-free survival; OS=overall survival  
Source: compiled during the evaluation.

6.27 In the base case of the model, the submission used a 10-year time horizon. This was not reasonable, given that the proposed population is advanced or metastatic non-squamous NSCLC patients who have progressed on first-line treatment. Previous submissions to the PBAC for other NSCLC treatments used a 5-year time horizon. The PSCR (p.3) maintained that 10 years was an appropriate time horizon, citing data from Gettinger et al (2015). The ESC noted, however, that the updated 4-year OS rate presented is █%, and considered that this data would support a 5-year rather than a 10-year time horizon. The PSCR further stated that age at entry of patients in CA209-057 ranged between 37 and 85 years of age, and that it was clinically plausible, primarily for the younger patients, to expect a proportion of this cohort to still be alive at 10 years of follow-up. The ESC considered that younger patients would generally have a poorer prognosis, and so a 10-year time horizon would not be appropriate.

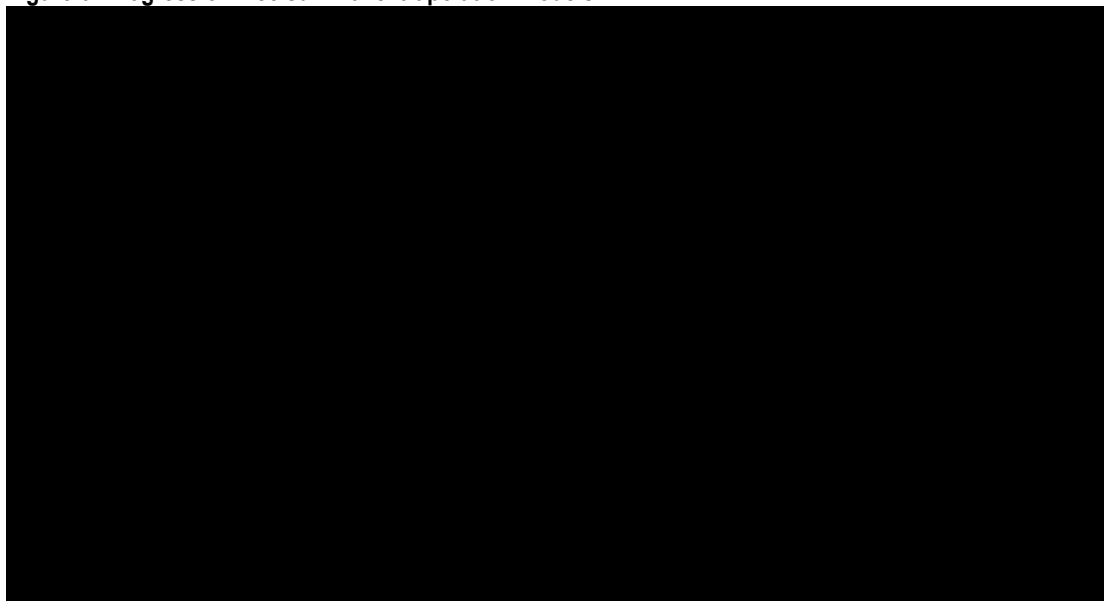
- 6.28 The submission used three methods to derive the time point from which to extrapolate the Kaplan-Meier OS and PFS curves of the CA209-057 trial. In the base case of the model, the submission used median time to follow-up based on the reverse Kaplan-Meier methodology (Schemper and Smith 1996, provided in the submission). Median duration of follow-up and the end of available Kaplan-Meier curves were used in sensitivity analyses.
- 6.29 The submission chose the log-logistic parametric distributions for extrapolation of both OS and PFS of nivolumab, log-logistic curve for docetaxel PFS and Weibull parametric distribution for docetaxel OS. The submission stated that these selections were based on both face validity and goodness of fit statistics. There was minimal difference in Akaike's Information Criterion (AIC) values between log-logistic and Weibull models, with AIC for log-logistic model being slightly lower than that for Weibull model. Visual inspection of the curves indicates that the extrapolation using log-logistic models is more optimistic in predicting OS than that using Weibull model for both treatment arms. The selection of a log-logistic model for OS in the nivolumab arm and a Weibull model in the docetaxel arm resulted in a more favourable OS prediction in the nivolumab arm, but a less favourable prediction in the docetaxel arm. Therefore the incremental cost-effectiveness ratio (ICER) was biased favouring nivolumab. The PSCR (p.4) maintained that the log-logistic function was the most appropriate. The ESC considered that the selection of the log-logistic function for nivolumab (most favourable to nivolumab) and the Weibull function for docetaxel (least favourable to docetaxel), overestimated the increments for both PFS and OS. The Pre-PBAC Response (p.3) acknowledged the sensitivity of the modelled economic evaluation to the parametric functions, however argued that "the log-logistic OS curve predicts 23% of patients will still be alive at 3 years, whereas the Weibull OS curve predicts 2.4% of patients will be alive at 3 years. Results from CA209-003, which reported data specific to non-squamous NSCLC patients demonstrated that 24% of patients are still alive at 3 years – thereby illustrating that application of the log-logistic function is clinically appropriate."

Figure 5: Overall survival extrapolation models



Source: Figure 24, Section C.3.3 of the submission.

**Figure 6: Progression-free survival extrapolation models**



Source: Figure 25, Section C.3.3 of the submission.

- 6.30 The model assumed that, after the truncation point, the PFS and OS curves would follow the chosen parametric functions continually until the end of the model. This was not reasonable in the absence of robust long term survival data from the patients treated with nivolumab. The submission should have provided a conservative modelling approach assuming the two OS curves converging within the time horizon. The PSCR (p.4) claimed that ‘the durable survival associated with nivolumab as reflected in the survival curve as “flattening” does not favour this approach’. The ESC considered the base case assumption to be implausible, particularly when combined with the 10-year time horizon.
- 6.31 Utilities were derived from CA209-057. 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.
- 6.32 Ongoing disease management costs were obtained from a Health Resource Utilisation (HRU) survey of 15 oncologists. The response rate was low (7/15 = 46.7%). Therefore the representativeness of the responses was uncertain. In the base case of the model, based on one clinician’s opinion, the submission assumed that during the pre-progression period, patients treated with nivolumab would only use 80% of the costs of health care resources of those treated with docetaxel, on the grounds of nivolumab’s better tolerability. The ESC agreed that relying on only one clinician’s opinion in deciding the pre-progression resource use in the nivolumab arm was inappropriate and biased the result of economic model in favour of nivolumab, although the impact on the ICER was low.
- 6.33 The submission also made arbitrary assumptions regarding pre-progression and post-progression resource use. The submission assumed that, during the post-progression period, the resource use generated from survey results was only

applicable to the first two years. In years 2-5 post-progression, the cost was halved and beyond 5 years, the cost was quartered. In the economic model, since patients treated with nivolumab had a longer post-progression survival than those treated with docetaxel, the reduced costs for long-term survivors favoured the nivolumab arm. The PSCR (p.5) cited follow-up after cancer treatment fact-sheets to argue that patients require less frequent follow-up over time, however the ESC considered that these patients would be disease-free survivors, and so were not relevant to the patients in the model who would progress and require increased resources.

6.34 The truncated mean durations of therapy, which were [REDACTED] infusions for nivolumab and [REDACTED] infusions for docetaxel, as observed in CA209-057, were used in the modelled economic evaluation. This was inappropriate and underestimated the costs of nivolumab and docetaxel. Given that health outcomes were been extrapolated for both the nivolumab and docetaxel arms in the model, treatment durations should have been extrapolated correspondingly. Since nivolumab was associated with a longer extrapolated PFS compared with docetaxel, using truncated trial-based treatment duration biased the results of economic evaluation in favour of nivolumab. Although the PSCR (p.4) maintained that these were the appropriate mean durations of therapy, the ESC considered that if the model extrapolates health outcomes over 10 years, then it should also extrapolate the costs of treatment linked to those health outcomes.

6.35 Results of the economic evaluation are presented below.

**Table 9: Results of the stepped economic evaluation**

Step and component	Nivolumab	Docetaxel	Increment
<b>Step 1 and Step 2: Within trial duration costs and outcomes</b>			
Costs*	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	1.18	1.03	0.15
QALYs	0.90	0.72	0.18
<b>Incremental cost/LY gained</b>			\$ [REDACTED]
<b>Incremental cost/QALY gained</b>			\$ [REDACTED]
<b>Step 3: modelled evaluation (extrapolating health outcome to 10 years, without extrapolating drug costs)</b>			
Costs*	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	2.00	1.22	0.77
QALYs	1.50	0.85	0.65
<b>Incremental cost/extra LY gained</b>			\$ [REDACTED]
<b>Incremental cost/extra QALY gained</b>			\$ [REDACTED]

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

Drug costs are based on ex-manufacturer's price.

Source: Table 72, Table 74 and Table 75, Section D.5 of the submission.

- 6.36 The largest cost component in the docetaxel arm was the 'ongoing disease management costs', which contributed as a cost-offset to the incremental cost difference between the two arms.
- 6.37 Extrapolating health outcomes to 10 years without extrapolating drug usage substantially decreased the ICER in favour of nivolumab.
- 6.38 The results of key sensitivity analyses are presented below.

**Table 10: 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.5: Method of extrapolation	Log-logistic for nivolumab and docetaxel PFS and OS#	\$ [REDACTED]	\$ [REDACTED]
	Weibull for nivolumab and docetaxel PFS and OS	\$ [REDACTED]	\$ [REDACTED]
SA.6: Utility value	Overall nivolumab and docetaxel utility values (not arm specific)	\$ [REDACTED]	\$ [REDACTED]
	Utility for progressive disease is assumed to be 0.59 in both arms*	\$ [REDACTED]	\$ [REDACTED]
SA.7: Ongoing disease management costs	Docetaxel and nivolumab pre-progression and post-progression costs equal	\$ [REDACTED]	\$ [REDACTED]
	Post-progression costs equal regardless of years spent in progressive disease	\$ [REDACTED]	\$ [REDACTED]
SA.8: Time horizon	5 years	\$ [REDACTED]	\$ [REDACTED]
	3 years	\$ [REDACTED]	\$ [REDACTED]
SA.9: Including drug wastage**	2 vials of 100 mg and 1 vial of 40 mg nivolumab	\$ [REDACTED]	\$ [REDACTED]
SA.8 + SA.9	5-year time horizon and including wastage of nivolumab	\$ [REDACTED]	\$ [REDACTED]
SA.5 + SA.8 + SA.9	5-year time horizon, including wastage of nivolumab and extrapolation using Weibull model for PFS and OS extrapolation in both arms (SA.10-1)	\$ [REDACTED]	\$ [REDACTED]
	5-year time horizon, including wastage of nivolumab and extrapolation using log-logistic model for PFS and OS extrapolation in both arms (SA.10-2)	\$ [REDACTED]	\$ [REDACTED]

# This was the extrapolation methods used in the base case of the model for nivolumab in the treatment of squamous NSCLC.

\* Based on utility value for the progressive disease from Chouaid et al (2013)<sup>e</sup>. When considering erlotinib in March 2014, the PBAC stated that utilities from Chouaid (2013) were more representative estimates (Item 7.3 erlotinib, Public Summary Document March 2014).

\*\* Wastage of docetaxel was already included in the base case, if assuming 1 × 140 mg vial is used. The allowance of wastage of docetaxel did not have a material impact on the results of the economic evaluation.

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

Source: Table 77, Section D.6 of the submission and additional analysis conducted during the evaluation.

- 6.39 Table 10 indicates that the model was sensitive to time horizon, point of extrapolation, method of extrapolation, utility values and the assumption that the disease management cost reduces substantially when patients survive more than 2 years post progression.
- 6.40 Time horizon and extrapolation methods had the most impact on the results of the economic evaluation. When using a 5-year time horizon, the ICER increased to \$75,000/QALY - \$105,000/QALY gained from the base case of \$45,000/QALY - \$75,000/QALY gained. When extrapolating the OS and PFS with log-logistic models in both arms, as used in the base case of the model for squamous NSCLC, the ICER increased to \$75,000/QALY - \$200,000/QALY gained. The ICER increased to \$105,000/QALY - \$200,000/QALY gained when extrapolating PFS and OS with Weibull models in both treatment arms.

<sup>e</sup> Chouaid C, Agulnik J, Goker E, Herder GJ, Lester JF, Vansteenkiste 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. J Thorac Oncol. 2013;8(8):997-1003.

- 6.41 Drug wastage should have been included in the base case of the model as this would reflect clinical practice. A 5-year or 3-year time horizon would be more reasonable than a 10-year horizon used in the base case. During the evaluation, multi-variate sensitivity analyses were conducted and suggested that, when assuming a 5-year time horizon and including drug wastage, the ICER increased to \$75,000/QALY - \$105,000/QALY gained. Additionally, when extrapolating PFS and OS using log-logistic model for both arms, the ICER further increased to \$105,000/QALY - \$200,000/QALY gained, while the ICER increased to \$105,000/QALY - \$200,000/QALY gained when using Weibull model to extrapolate both PFS and OS in both arms.

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

- 6.42 The total drug cost per patient is at least \$ [REDACTED]. This was calculated using the proposed effective dispensed price and assuming the average body weight of 72.2 kg for a patient, requiring 216.6 mg of nivolumab, supplied from 2 × 100 mg vials and 1 × 40 mg vial of nivolumab (allowing for wastage), with [REDACTED] infusions, as observed from CA209-057 (without any extrapolation over time). It was also assumed that 13% of the drug would be dispensed in public hospitals and 87% in private hospitals. This is compared with a total cost of approximately \$ [REDACTED] for treatment with docetaxel, based on its usage in CA209-057.

**Estimated PBS usage & financial implications**

- 6.43 This submission was considered by DUSC. The submission took an epidemiological approach to estimate the number of patients with non-squamous NSCLC each year and the proportion of patients eligible for EGFR TKIs or ALK inhibitors based on the literature. The submission further estimated the proportion of patients treated with each second- or later-line therapies based on expert opinion.
- 6.44 There was considerable uncertainty in the proportions of patients assumed to receive each treatment option, given that they 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.
- 6.45 The total cost of nivolumab was likely to be an underestimate since the treatment duration was assumed to be as that observed in CA209-057. The trial duration was unlikely to be sufficient to capture the full treatment duration. The estimated use and financial implications of nivolumab in the treatment of non-squamous NSCLC are summarised below. The net cost to the PBS/RPBS over five years was estimated to be more than \$100 million.

**Table 11: Estimated extent of nivolumab use and associated costs to the PBS**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Patients treated with nivolumab	████	████	████	████	████
Number of vials <sup>b</sup>					
100mg/mL <sup>a</sup>	████	████	████	████	████
40mg/4mL (wastage included) <sup>a</sup>	████	████	████	████	████
<b>Estimated drug cost to the PBS and RPBS</b>					
Cost to the PBS/RPBS (including wastage) <sup>a,b,c</sup>	\$████	\$████	\$████	\$████	\$████
<b>Estimated cost offsets from drug substitutions</b>					
Reduction in patients using docetaxel due to nivolumab	████	████	████	████	████
Reduction in patients using pemetrexed due to nivolumab	████	████	████	████	████
Estimated cost offsets due to docetaxel and pemetrexed substitutions <sup>d</sup>	\$████	\$████	\$████	\$████	\$████
<b>Overall cost to the PBS/RPBS</b>					
Overall net cost <sup>a,b,c</sup>	\$████	\$████	\$████	\$████	\$████
<b>Estimated cost to the MBS from drug administrations</b>					
Number of administrations <sup>a</sup>	████	████	████	████	████
Reduction in the number of administrations for docetaxel and pemetrexed, combined	████	████	████	████	████
At full benefit amount	\$████	\$████	\$████	\$████	\$████
<b>Net cost to MBS (at 85% benefit)</b>	<b>\$████</b>	<b>\$████</b>	<b>\$████</b>	<b>\$████</b>	<b>\$████</b>

Source: Commentary on the main submission, Tables E.2.5 (p86), E.3.1 (p87) and E.5.1 (p89).

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

<sup>b</sup> Assuming on average one patient needs 216.6mg of nivolumab with a body weight of 72.2kg. To supply 216.6mg of nivolumab, 2 × 100mg/10mL vials and 0.42 × 40mg/4mL vials were assumed in the submission. During the evaluation, 2 × 100mg/mL vials and 1 × 40mg/4mL vial were used in the sensitivity analysis.

<sup>c</sup> The dispensed price of nivolumab was updated during the evaluation including a 1.4% pharmacy mark-up for private hospitals and the preparation fee of \$102.67.

<sup>d</sup> The dispensed prices of docetaxel and pemetrexed were updated during the evaluation including a 1.4% pharmacy mark-up for private hospitals and the preparation fee of \$102.67.

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

6.46 DUSC considered the estimates presented in the submission may be overestimated. The main issues were:

- The financial implications to government may be overestimated by applying a 'wider' versus 'narrower' definition of NSCLC to estimate the non-squamous NSCLC eligible population (81.7% vs. 74.2%, respectively). The Pre-PBAC

Response (p.3) acknowledged that there is uncertainty regarding the true split between squamous and non-squamous NSCLC patients in Australia, noting that an “if a narrower definition of NSCLC is used (excluding less common NSCLC subtypes), then the estimate of the proportion of squamous NSCLC patients reduces to 74.2% and net cost to the PBS decreases.”

- The duration of nivolumab treatment in practice would likely be longer than the estimate based on Trial 057 due to the early cessation of this trial.
- There was potential for use beyond the restriction: (i) use in earlier lines of therapy; (ii) use in patients with a performance status that is worse than those participating in the key trial (i.e. ECOG >1); and (iii) use beyond disease progression.

### **Quality Use of Medicines**

- 6.47 Given the need (at least in the short term as noted in the submission) for close attention to the early identification and appropriate treatment of immune-related adverse reactions, the submission provided a summary of the sponsor’s plans regarding the quality use of medicines. This included a support and educational framework for practitioners and patients and other initiatives supporting nivolumab use in Australian clinical practice.

### **Financial Management – Risk Share Arrangements**

- 6.48 The submission proposed a Special Pricing Arrangement (SPA) where the published price would be greater than the effective price. The submission also stated that the sponsor would commit to negotiations to manage residual uncertainty with respect to expenditure.

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

## **7 PBAC Outcome**

- 7.1 The PBAC decided not to recommend that nivolumab be listed in the PBS for the treatment of non-squamous NSCLC on the PBS on the basis that the cost-effectiveness against pemetrexed, which the PBAC considered to be a relevant main comparator, could not be determined because an economic comparison was not presented; and that acceptable cost-effectiveness against the submission’s nominated main comparator, docetaxel, had not been adequately demonstrated. The PBAC considered that the economic model presented in the submission included numerous assumptions that favoured nivolumab, and that the resulting incremental cost-effectiveness ratio was high and likely to be significantly underestimated.
- 7.2 The PBAC recognised that there is a clinical need for new treatments for patients with NSCLC, and that there is a clinical place for nivolumab in this population. The PBAC noted that the submission requested a second-line PBS listing for nivolumab, following progression on or after platinum-based chemotherapy.
- 7.3 The PBAC considered the following with regard to the requested restriction:
- that the continuing treatment restriction would need to contain the criterion

already used for PD-1 inhibitors requiring stable or responding disease whilst acknowledging early “pseudo-progression”;

- that the patient’s performance status would need to be 0 or 1, consistent with the eligibility criteria of the key clinical trial;
- should evidence be forthcoming on the use of biomarkers (such as PD-L1 expression) on treatment selection then further consideration should be given to the ESC’s view regarding the possibility of restricting nivolumab to patients who are PD-L1 positive.

- 7.4 The submission nominated docetaxel as the main comparator. The PBAC considered that for non-squamous NSCLC, pemetrexed was the main comparator. Although pemetrexed was identified as a minor comparator in the submission, an economic analysis against pemetrexed was not presented.
- 7.5 The PBAC noted that the key clinical trial, CA209-057, directly compared nivolumab and docetaxel, and the risk of bias was low for the outcome of overall survival. The PBAC noted that the mean age in trial CA209-057 was 61 years, which may not be representative of the Australian population with lung cancer, which has a mean age at diagnosis of more than 70 years. The PBAC considered that this difference between the trial and proposed PBS population would have implications for the estimation of comparative benefits and utilisation.
- 7.6 The PBAC noted that the proportional hazards assumption was not met, and that the nivolumab and docetaxel survival curves crossed with an initial increase and a subsequent decrease in hazard of death associated with nivolumab compared with docetaxel. Therefore the estimated hazard ratio, as a measure of the relative treatment effect or reduction in risk, could not be relied upon given the measure’s dependency on follow-up time. The PBAC therefore primarily relied on the statistically significant log rank test (which is not affected by these survival curves crossing) to accept the claim of superior comparative effectiveness.
- 7.7 The PBAC considered the evidence for treatment effect variation by PD-L1 status in trial CA209-057, noting that nivolumab was associated with median OS more than twice than that observed for docetaxel in PD-L1 positive patients, however median OSs were similar for nivolumab and docetaxel in PD-L1 negative patients. The PBAC concluded that this qualitative difference in clinical benefit constituted a signal suggesting important treatment effect variation according to PD-L1 testing as conducted in this trial.
- 7.8 However, the PBAC agreed with the sponsor, that the applicability of these subgroup results to the PBS setting was presently uncertain given the reliance on insufficiently developed testing for PD-L1 expression. The PBAC considered that, at present, there would be substantial challenges to accurately conducting and interpreting testing in Australia. Evidentiary challenges include: validating the biomarker itself (PD-L1 expression); conducting an independent analytical validation of the several immunohistochemistry assays for PD-L1 expression testing using different antibodies and different platforms under development by different companies; determining whether PD-L1 expression testing should be confined to tumour tissue and/or surrounding cells; validating the threshold scores which would be “positive” for initiating nivolumab (or any PD-1 inhibitor); and addressing the known heterogeneity of expression within tumours, across primary tumours and metastases, across time,

and after different interventions. Practical challenges include obtaining appropriate biospecimens for testing from patients at the point in the clinical pathway when therapy with a PD-1 inhibitor might be indicated, and the limited availability of the commercial platforms being developed. Evaluating the clinical utility of the PD-L1 as a predictive biomarker also required an assessment of its relationship to the endpoint of interest (survival) and the consistency of this relationship in different tumour types and across studies (Mahoney et al, *Oncology* 2014; 28(Suppl 3):39-48; Gandini et al, *Critical Reviews in Oncology / Hematology* 2016; 100:88-98, Advanced online publication. doi:10.1016/j.critrevonc.2016.02.001).

- 7.9 The PBAC considered that the claim of superior comparative safety of nivolumab over docetaxel was reasonable, however also noted that nivolumab was associated with a significantly higher proportion of patients with Grade 3 and 4 endocrine adverse events than docetaxel.
- 7.10 The PBAC noted that pemetrexed was included in the financial analyses, however a cost-effectiveness analysis of nivolumab versus pemetrexed was not presented. This was important, because the PBAC judged pemetrexed to be the main comparator, which is currently being used more extensively than docetaxel in the patients proposed for this nivolumab listing, and also more likely to be substituted by nivolumab if nivolumab were listed. The PBAC considered that, on the basis that pemetrexed is more effective, less toxic and more expensive than docetaxel, its omission from the comparison had an unknown but potentially important effect on the economic evaluation.
- 7.11 The PBAC considered that the incremental cost per QALY gained of \$45,000/QALY - \$75,000/QALY for nivolumab over docetaxel presented in the submission's base case analysis was high, and was likely to be significantly underestimated due to several concerns raised by the ESC regarding the economic model, including:
- time horizon: the submission used a ten-year time horizon, however the PBAC agreed with the ESC (see paragraph 6.27) that a five-year time horizon would be more appropriate;
  - the method of extrapolation: selection of the log-logistic function for nivolumab (most favourable to nivolumab) and the Weibull function for docetaxel (least favourable to docetaxel), inappropriately overestimated the increments for both PFS and OS;
  - the extrapolated PFS and OS curves follow parametric functions until the end of the model, when a more appropriate approach would have been to assume the two OS curves converge within the time horizon;
  - the assumptions applied regarding treatment duration and costs of ongoing disease management favoured nivolumab.
- 7.12 The PBAC noted that the estimated net cost of nivolumab for squamous NSCLC was more than \$100 million over five years. The PBAC noted the DUSC's concerns regarding the eligible patient numbers, duration of treatment in practice, and potential risk of use beyond the restriction, and advised that a financial cap would be required to manage these uncertainties.

- 7.13 The PBAC considered that any resubmission should be a major submission to allow for evaluation of an improved economic model which included pemetrexed as the main comparator.
- 7.14 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 is working to ensure timely PBS listing of nivolumab for Australian patients with non-squamous NSCLC.