

**5.06 NIVOLUMAB, 40 mg/4 mL vial, 100 mg/10 mL vial, OPDIVO[®],
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 squamous non-small cell lung cancer (NSCLC). The PBAC also considered a concurrent submission to list nivolumab for non-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.

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

^a 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)¹. The submission proposed a special pricing arrangement.

Category / Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Locally advanced or metastatic
Condition:	Squamous squamous non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced or metastatic squamous squamous non-small cell lung cancer (NSCLC)
Treatment phase:	Initial treatment
Restriction Level / Method:	<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
Clinical criteria:	<i>The condition must be squamous type non-small cell lung cancer (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>
Prescriber Instructions:	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

¹ Preparation fee of \$102.67 has been used

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Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Locally advanced or metastatic
Condition:	Squamous non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)
Treatment phase:	Continuing treatment
Restriction Level / Method:	<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
Clinical criteria:	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.
Prescriber Instructions:	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

- 2.2 The submission also requested that grandfathering of patients from the early nivolumab access program be permitted upon implementation of PBS listing.
- 2.3 The requested restriction does not specify performance status, although the key trial only included patients with a performance status of 0 or 1.
- 2.4 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 CA209-017 trial, approximately 20% of nivolumab-treated patients were allowed to continue treatment beyond RECIST defined progression until “further progression” based on a 10% increase in tumour burden volume from initial RECIST defined progression. 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 Pre-Sub-Committee Response (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 Nivolumab was submitted to the TGA for evaluation on 7 January 2015. The dossier included trial data for the treatment of melanoma, squamous and non-squamous NSCLC. According to the letter of approval from the TGA delegate dated 7 January 2016, the approved TGA indication, relevant for the current submission, is “as monotherapy for the treatment of locally advanced or metastatic squamous NSCLC, with progression on or after prior chemotherapy”.
- 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. The standard first-line therapy for squamous NSCLC patients is platinum-based doublet chemotherapy.
- 4.2 The intended listing was for patients who have failed platinum-based chemotherapy, thus displacing docetaxel monotherapy further down the treatment algorithm. The proposed mechanism of action of nivolumab was that it blocks programmed cell death-1 (PD-1) inhibition of the immune system and prevents ligand binding. However, the submission did not propose restricting nivolumab to squamous NSCLC patients with PD-L1 expression (PD-L1 positive). The submission emphasised that PD-L1 expression is likely not an appropriate immune marker, interpretation of PD-L1 expression testing varies, and all patients benefited from nivolumab treatment over docetaxel regardless of PD-L1 status. The ESC advised that, should nivolumab be listed for NSCLC, then it should be restricted to patients who are PD-L1 positive, and should cover all histological subtypes of NSCLC. The Pre-PBAC Response (p.1) strongly disagreed that PBS-listed nivolumab should be restricted to patients who are PD-L1 expression positive, and claimed that this would be inconsistent with the clinical data presented. The Pre-PBAC Response further stated that “squamous and non-squamous NSCLC histological subtypes arise in different anatomical compartments – for example, squamous NSCLC may often arise from the central

airway compartment (i.e. close to large vessels). This may explain why some therapies might be more effective in non-squamous NSCLC compared to squamous NSCLC". The ESC noted that a Phase III trial of nivolumab vs investigator's choice chemotherapy as first-line therapy for Stage IV or recurrent PD-L1 positive NSCLC (Checkmate 026) is underway, which may reflect an expectation that nivolumab may be more effective in the subgroup of patients with PD-L1 positive status. The Pre-PBAC Response (p.2) stated that "at the time CheckMate 026 was designed several years ago with the hypothesis that there might be a larger role for selecting patients on the basis of PD-L1 expression in first line (where ~70% patients are PD-L1 positive) than in second line (where ~ 50% patients are PD-L1 positive). As such, the trial eligibility criteria for CheckMate 026 was limited to PD-L1≥1% patients. Given the results of study CA209017, this hypothesis is no longer valid."

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

5 Comparator

- 5.1 The submission nominated docetaxel as the main comparator. This is the appropriate comparator.

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 what level of performance status would be suitable for nivolumab treatment, the likely role of nivolumab as monotherapy, sequential therapy or combination therapy, and 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 (CA209-017: N=272) comparing nivolumab with docetaxel in previously treated patients with locally advanced or metastatic squamous NSCLC.

6.4 Details of the trial presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
CA209-017	<p>Clinical study report CA209-017: An open-label randomised 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><u>Publication</u> 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> 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>February 2015</p> <p><i>New England Journal of Medicine</i> 2015; 373 (2):123-132</p> <p><i>16th World Conference on Lung Cancer</i>; Denver, USA, September 6-9, 2015.</p>

Source: Table 11, p35 of Section B.2 of the submission.

6.5 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
Nivolumab 3 mg/kg Q2W vs. docetaxel 75mg/m² Q3W						
CA209-017	582	R, OL Database lock December 2014 (follow-up 10.6 months) and database lock August 2015 (most updated: follow-up 18 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 minimal confounding of the overall survival (OS) results as there was minimal treatment switching. Randomisation was fairly successful as there was a reasonable balance of baseline characteristics across treatment arms. 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. Knowledge of treatment allocation may also have affected patients' subjective responses to quality of life questionnaires.

Comparative effectiveness

6.7 The clinically relevant outcome to determine patient benefit in CA209-017 was overall survival (OS). Table 3 summarises the OS results from the database lock in December 2014 (minimum follow up 10.6 months) and the database lock in August 2015 (most updated: minimum follow-up 18 months). The Kaplan-Meier curves for

OS (18 month follow up) are presented in Figure 1. The Kaplan-Meier OS rates at 6 months, 12 months and 18 months are summarised in Table 4.

Table 3: CA209-017 - Overall survival (OS) results

	CA209-017 CSR Database Lock December 2014 (10.6 months minimum follow-up)		CA209-017 - Updated OS ¹ Database Lock August 2015 (18 months minimum follow-up)	
	Nivolumab N=135	Docetaxel N=137	Nivolumab N=135	Docetaxel N=137
Number of events, n (%)	86 (63.7)	113 (82.5)	103 (76.3)	122 (89.05)
Median (months) (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)	9.2 (7.3, 12.6)	6.0 (5.3, 7.4)
Nivolumab versus docetaxel Stratified HR; stratified log-rank: p-value	0.59 (96.85% CI: 0.44, 0.79) ² ; p=0.0004		0.62 (95%CI: 0.48, 0.81); p=0.0004	

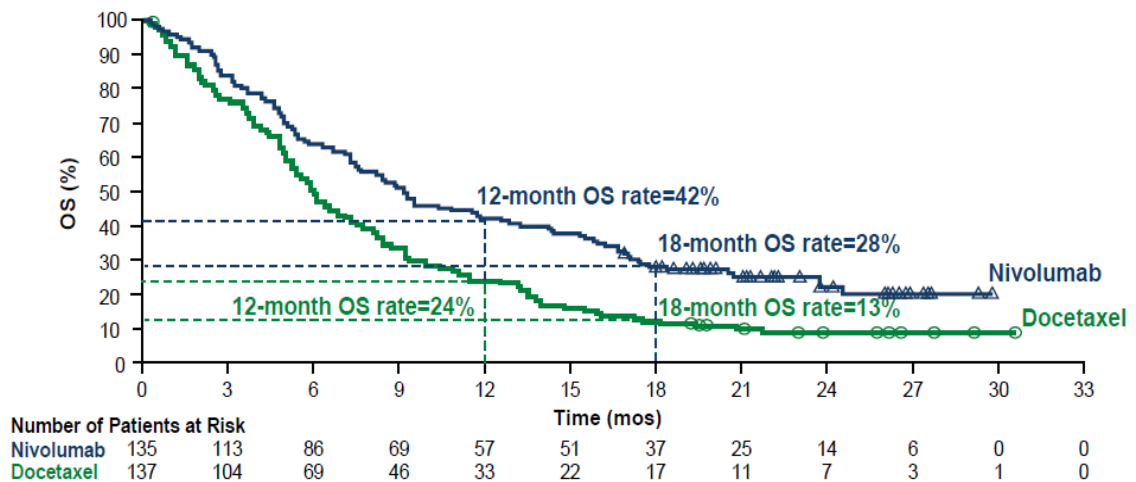
¹ Reckamp et al (2015); Reckamp, R et al (2015). Phase 3, Global, Randomized trial (Checkmate 017) of nivolumab vs docetaxel in advanced squamous cell non-small cell lung cancer (NSCLC) - 16th World Conference on Lung Cancer, September 6 – 9, Denver, USA

² Based on the 199 observed deaths and O'Brien-Fleming alpha spending function, the nominal significance level for declaring OS superiority during the pre-planned interim analysis was p<0.0315, and therefore a 96.85% CI for the OS HR (CA209-017 CSR, p98).

CSR=clinical study report; CI=confidence interval; HR=hazard ratio

Source: Table 24, p58 of the main submission.

Figure 1: CA209-017 - Kaplan-Meier curves for overall survival (minimum 18 months follow-up)



Source: Figure 8, p59 of the main submission.

Table 4: CA209-017 - Kaplan-Meier overall survival rates at 6, 12 and 18 months

	6 months		12 months		18 months	
	NIVO	DOC	NIVO	DOC	NIVO	DOC
N	135	137	135	137	135	137
Database lock	15 December 2014				August 2015	
Estimated number of patients alive ^a : n (%) [95% CI]	86 (63.7) [NR, NR]	69 (50.4) [NR, NR]	57 (42.1) [33.7, 50.3]	32 (23.7) [16.9, 31.1]	38 (28.0) [NR, NR]	18 (13.0) [NR, NR]
OR [95% CI]; p-value	1.73 [1.06, 2.81]; p=0.03		2.40 [1.42, 4.04]; p=0.001		2.59 [1.39, 4.82]; p=0.003	
RR [95% CI]; p-value	1.26 [1.03, 1.56]; p=0.03		1.81 [1.26, 2.60]; p=0.001		2.14 [1.29, 3.56]; p=0.003	
RD [95% CI]; p-value	0.13 [0.02, 0.25]; p=0.02		0.19 [0.08, 0.30]; p=0.0007		0.15 [0.06, 0.24]; p=0.002	

CI=confidence interval; DOC=docetaxel; NIVO=nivolumab; NR=not reported; OR=odds ratio; RD=risk difference; RR=risk ratio

^a based on KM survival rate

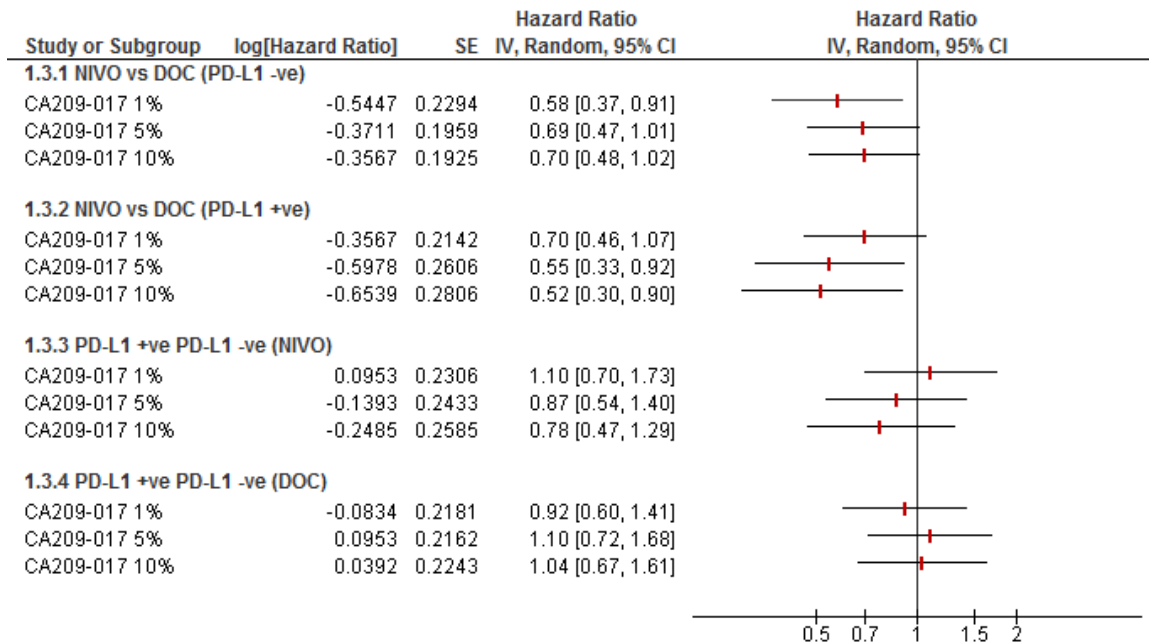
Source: Table 25, p60 of the main submission.

- 6.8 Compared with docetaxel, nivolumab was associated with a statistically significant 41% reduction in the risk of death (HR=0.59 [96.85% CI: 0.43, 0.81]; p=0.0002) in the analysis from the database lock in December 2014 after a minimum of 10.6 months follow-up. This reduction was similar in the analysis from the database lock at August 2015 after a minimum of 18 months of follow-up (HR=0.62 [95% CI: 0.48, 0.81]; p=0.0004). The difference in median OS between treatments at both follow up periods was 3.2 months, favouring nivolumab.

Treatment effect variation of nivolumab by PD-L1 status

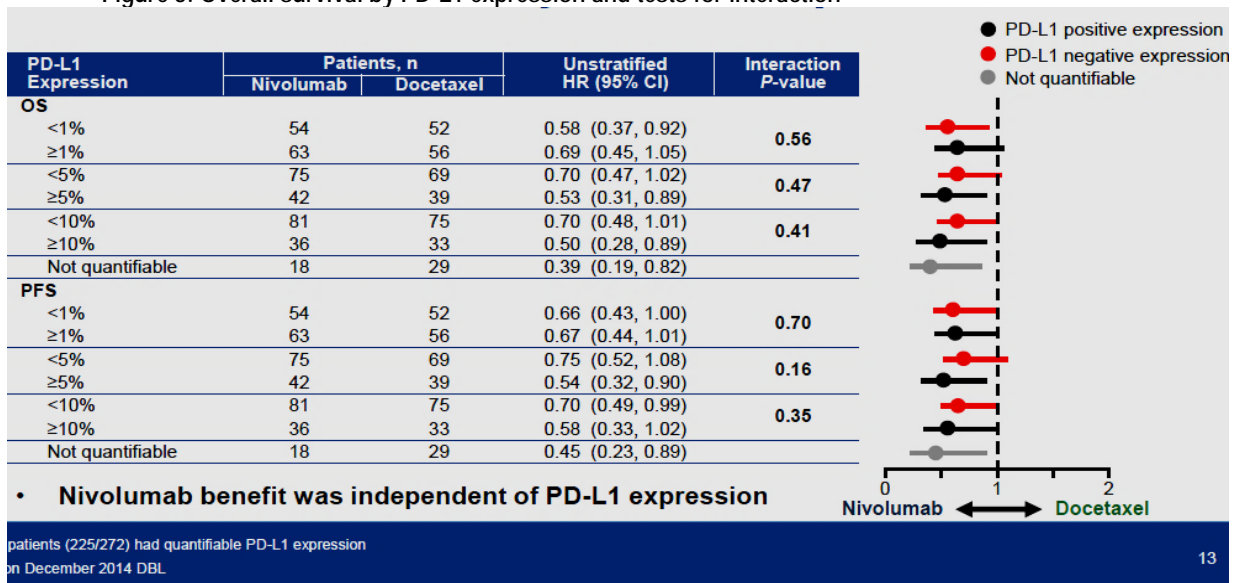
- 6.9 The submission did not specify PD-L1 positive expression as an eligibility criterion in the proposed PBS restriction for nivolumab. The argument presented in the submission was that all patients benefited from nivolumab treatment over docetaxel regardless of PD-L1 status. The results are summarised in Figures 2, 3 and 4 below. Tests for interaction were not statistically significant for any PD-L1 cut-off expression levels (Figures 2 and 3). The submission concluded that there was a statistically significant benefit in OS over docetaxel at negligible PD-L1 expression levels (PD-L1 <1%). Approximately 13% and 21% of patients in the nivolumab and docetaxel treatment arms, respectively, did not have PD-L1 quantifiable results. It was in these patients that nivolumab had the numerically largest benefit in OS and progression-free survival (PFS) (Figure 3). Furthermore, 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. These issues, in addition to the inherent limitations of subgroup analyses, make interpretation of the results problematic. However, there was no clear predictive effect of PD-L1 status on the comparative effectiveness of nivolumab, although the data indicated a trend toward increased benefit of nivolumab, over docetaxel, with increasing levels of PD-L1 expression.

Figure 2: Forest plot of the predictive relationship of baseline PD-L1 status for overall survival



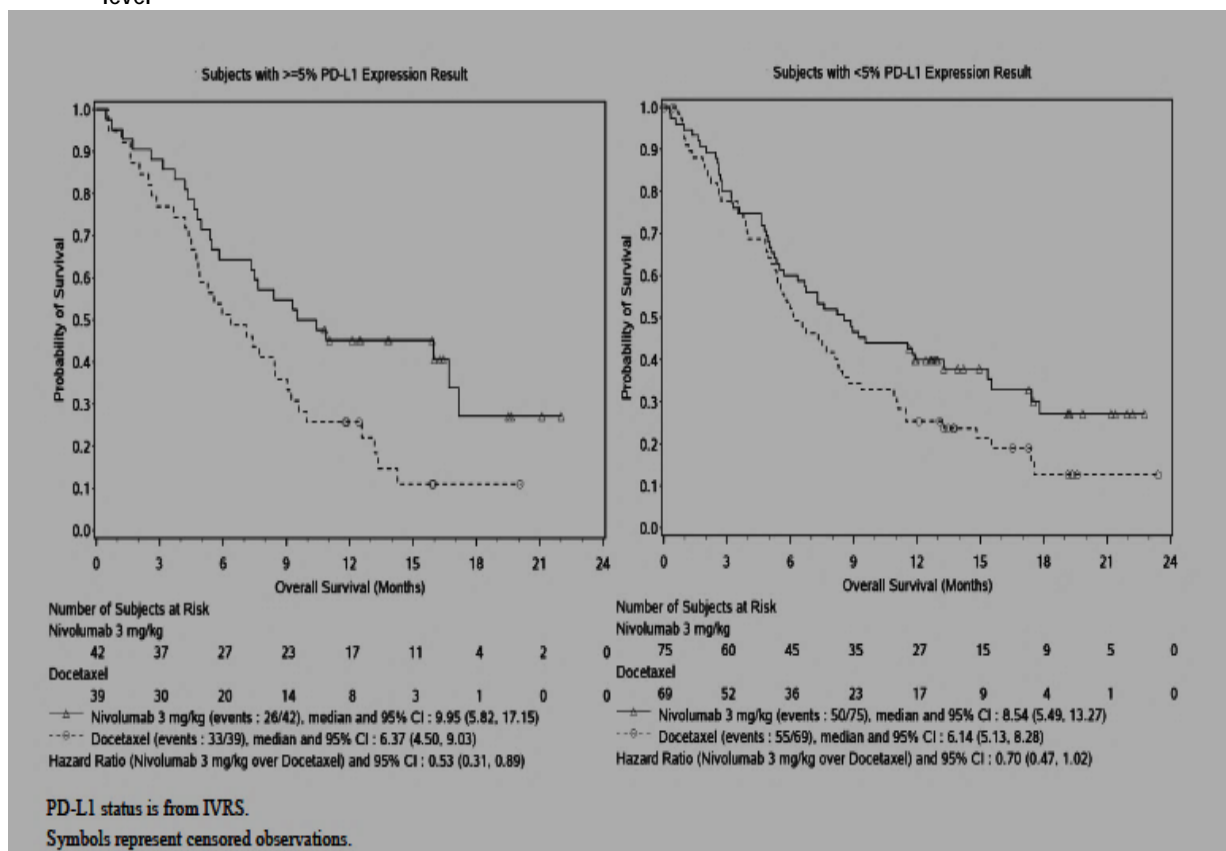
Nivo=nivolumab; DOC=docetaxel
Source: Figure 11, p63 of the main submission.

Figure 3: Overall survival by PD-L1 expression and tests for interaction



DBL=Database lock; HR=hazard ratio; CI=confidence interval; OS=overall survival; PFS=progression-free survival
Source: Reckamp et al (2015); Reckamp, R et al (2015). Phase 3, Global, Randomized trial (Checkmate 017) of nivolumab vs docetaxel in advanced squamous cell non-small cell lung cancer (NSCLC) - 16th World Conference on Lung Cancer, September 6 – 9, Denver, USA.

Figure 4: CA209-017 - Kaplan-Meier plot of overall survival by PD-L1 expression status at the 5% cut-off level



Source: Figure 7.6.1-1, p120 of the clinical study report.

- 6.10 The impact of PD-L1 expression on OS is much less clear than in the recent trial data in non-squamous NSCLC (Trial CA209-057 - presented as key evidence in a concurrent nivolumab submission to the PBAC), where there was a statistically significant predictive effect of PD-L1 status on the comparative effectiveness of nivolumab. Analysis of OS data from CA209-057 showed there was no difference in median OS between nivolumab and docetaxel for PD-L1 negative patients ($< 1\%$, $< 5\%$ and $< 10\%$ expression levels) whilst for PD-L1 positive patients ($\geq 1\%$, $\geq 5\%$, and $\geq 10\%$ expression levels), nivolumab was associated with median OS estimates more than twice that observed for docetaxel (18-20 months vs 8-9 months).

Comparative harms

- 6.11 The tables below provide a summary of adverse events (AEs) from CA209-017.
- 6.12 The submission conducted numerous statistical comparisons of the frequency of AEs between the nivolumab and docetaxel treatment arms. However, it was not apparent from the submission whether there was any adjustment for multiple comparisons to minimise the risk of a Type 1 error. Putative statistically significant findings need to be cautiously interpreted when there is no adjustment for multiple statistical analyses. There were no statistically significant differences in “any cause” AEs between the nivolumab and docetaxel treatment arms. For drug-related severe (\geq Grade 3), serious AEs and AEs leading to discontinuation, the differences were statistically

significant and favoured nivolumab. Significantly more drug-related severe AEs were reported in the docetaxel treatment arm as compared with the nivolumab treatment arm (57% vs. 7%), specifically for neutropenia (30% versus 0%). These differences in AEs were similar to those observed in the nivolumab non-squamous CA209-057 trial presented as key evidence in a concurrent submission to the PBAC. These safety data would need to be interpreted within the context of the open-label design of the nivolumab trials.

Table 5: CA209-017 - Summary of overall adverse events

Treatment arm N	NIVO	DOC	RR	RD
	131	129		
One or more AE - n (%)				
Any cause	127 (96.9)	125 (96.9)	1.00 [0.96, 1.04], p=0.98	0.00 [-0.04, 0.04], p=0.98
Study drug-related	76 (58.0)	111 (86.0)	0.67 [0.57, 0.79], p<0.00001	-0.28 [-0.38, -0.18], p<0.00001
SAE -n (%)				
Any cause	61 (46.6)	70 (54.3)	0.86 [0.67, 1.09], p=0.22	-0.08 [-0.20, 0.04], p=0.21
Study drug-related	9 (6.9)	31 (24.0)	0.29 [0.14, 0.58], p=0.0005	-0.17 [-0.26, -0.09], p<0.0001
Severe AE (Grade ≥3) n (%)				
Any cause	9 (6.9)	20 (15.5)	0.44 [0.21, 0.94], p=0.03	-0.09 [-0.16, -0.01], p=0.03
Study drug-related	2 (1.5)	9 (7.0)	0.22 [0.05, 0.99], p=0.05	-0.05 [-0.10, -0.01], p=0.03
AE leading to treatment discontinuation, n (%)				
Any cause	14 (10.7)	26 (20.2)	0.53 [0.29, 0.97], p=0.04	-0.09 [-0.18, -0.01], p=0.03
Study drug-related	4 (3.1)	13 (10.1)	0.30 [0.10, 0.90], p=0.03	-0.07 [-0.13, -0.01], p=0.02

Statistically significant differences bolded.

AE=adverse event; SAE=serious adverse event; DOC=docetaxel; NIVO=nivolumab; OR=odds ratio; RD=risk difference; RR=risk ratio

Source: Table 31, p73 of the submission.

Table 6: CA209-017 - Most frequent severe specific adverse events (≥Grade 3)

Treatment arm N	NIVO	DOC	RR	RD
	131	129		
All cause (severe AEs reported in at least 5% of any treatment arm) - n (%)				
One or more severe AE	67 (51.1)	94 (70.5)	0.70 [0.58, 0.86], p=0.0005	-0.22 [-0.33, -0.10], p=0.0002
Dyspnoea	7 (5.3)	8 (6.2)	0.86 [0.32, 2.31], p=0.77	-0.01 [-0.07, 0.05], p=0.77
Fatigue	3 (2.3)	11 (8.5)	0.27 [0.08, 0.94], p=0.04	-0.06 [-0.12, -0.01], p=0.03
Asthenia	0 (0)	9 (7.0)	0.05 [0.00, 0.88], p=0.04	-0.07 [-0.12, -0.02], p=0.003
Pneumonia	9 (6.9)	8 (6.2)	1.11 [0.44, 2.78], p=0.83	0.01 [-0.05, 0.07], p=0.83
Neutropenia	1 (0.8)	38 (29.5)	0.03 [0.00, 0.19], p=0.0003	-0.29 [-0.37, -0.21], p<0.00001
Febrile neutropenia	0 (0)	12 (10.1)	0.04 [0.00, 0.66], p=0.02	-0.09 [-0.14, -0.04], p=0.0004
Malignant neoplasm progression	14 (10.7)	9 (7.1)	1.53 [0.69, 3.41], p=0.30	0.04 [-0.03, 0.11], p=0.29
Study drug-related (severe AEs reported in at least 5% of any treatment arm) - n (%)				
One or more AE	9 (6.9)	74 (57.4)	0.12 [0.06, 0.23], p<0.00001	-0.50 [-0.60, -0.41], p<0.00001
Fatigue	1 (0.8)	10 (7.8)	0.10 [0.01, 0.76], p=0.03	-0.07 [-0.12, -0.02], p=0.005
Neutropenia	0 (0)	38 (29.5)	0.01 [0.00, 0.21], p=0.002	-0.29 [-0.37, -0.22], p<0.00001
Febrile neutropenia	0 (0)	13 (10.1)	0.04 [0.00, 0.61], p=0.02	-0.10 [-0.15, -0.05], p=0.0002

Statistically significant differences bolded.

AE = adverse event; DOC = docetaxel; NIVO = nivolumab; OR = odds ratio; RD = risk difference; RR = risk ratio

Source: Table 33, p78 of the main submission.

- 6.13 The CA209-017 CSR presented data on Grade ≥ 3 “Select AEs”² (AEs of special interest that were potentially associated with the use of nivolumab). Nivolumab was associated with a slightly higher proportion of Grade ≥ 3 endocrine AEs [9/131 (6.9%) vs. 3/129 (2.3%)] and a lower proportion of gastrointestinal events 21/131 (16.0%) vs. 33/129 (25.6 %)] compared with docetaxel.

Benefits/harms

- 6.14 A summary of the comparative benefits and harms for nivolumab versus docetaxel in the ITT squamous NSCLC population (unselected for PD-L1 expression) is presented in the table below. Tests for proportional hazards indicated that this assumption was met. Comparative benefits or harms, by PD-L1 status, are not presented in the table. Tests for treatment effect variation, by PD-L1 status, were not statistically significant, but the analyses suggested a trend towards some predictive effect.

² Choice of Select AEs was based on 4 guiding principles: 1) AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies, 2) AEs that may require immunosuppression (e.g., corticosteroids) as part of their management, 3) AEs whose early recognition and management may mitigate severe toxicity, and 4) AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterisation.

Table 7: CA209-017: 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		
Benefits						
Overall survival (OS)						
Kaplan-Meier OS rate ^a at 12 months (Database lock: December 2014)	57/135	32/137	42 (34, 50)	24.0 (17, 31)	18 (8, 30)	
Kaplan-Meier OS rate ^a at 18 months ^b (Database lock: August 2015)	38/135	18/137	28 (NR)	13 (NR)	15 (6, 24)	
	Nivolumab	Docetaxel	Absolute difference		HR (95% CI)	
Median OS, months (95% CI) (August 2015 database lock, 18 months follow up) ^c	9.20 (7.33, 12.62)	6.00 (5.29, 7.39)	3.20		0.62 (0.48, 0.81)	
Harms (Safety set)						
	Nivolumab	Docetaxel	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Nivolumab	Docetaxel	
Drug related severe AEs (Grade ≥3)	2/131	9/129	0.22 (0.05, 0.99)	1.5	7.0	-0.05 (-0.10, -0.01)
Drug related serious AEs (Grade ≥3)	9/131	31/129	0.29 (0.14, 0.58)	6.9	24.0	-0.17 (-0.26, -0.09)
Grade ≥3 drug-related neutropenia	0/131	38/129	0.00 (0.00)	0.0	29.5	-0.29 (-0.37, -0.22)
"Select" ^d Grade 3-4 endocrine related AEs	9/131	3/129	2.95 (0.87, 10.00)	6.9	2.3	0.05 (-0.01, 0.10)

^a Numerator calculated from proportions provided in the submission and total number of patients randomised to treatment arm.
^b Data sourced from Reckamp et al (2015): 16th World Conference on Lung Cancer. September 6 – 9. 2015. Denver, USA.
^c Median OS and HRs were similar for both the December 2014 (10.6 months minimum follow up) and August 2015 (18 months minimum follow up) database locks.
^d Select AEs were AEs of special interest that were potentially associated with the use of nivolumab (sourced from the CA209-017 clinical study report).
 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.

- 6.15 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 ≥3 neutropenia, but 5 more patients would experience endocrine-related AEs.

Clinical claim

- 6.16 The submission described nivolumab as superior in terms of comparative effectiveness and superior in terms of comparative safety over docetaxel for the treatment of locally advanced or metastatic squamous NSCLC with progression on or after prior platinum doublet chemotherapy. This claim is reasonable based on the

results from CA209-017. However, nivolumab is likely to be associated with a higher rate of severe AEs in current clinical practice until there is adequate familiarity with its use (see quality use of medicines section below).

- 6.17 The ESC considered that the submission’s claim of superior comparative effectiveness and superior comparative safety over docetaxel was reasonable.
- 6.18 The PBAC considered that the claim of superior comparative effectiveness over docetaxel was reasonable.
- 6.19 The PBAC considered that the claim of superior comparative safety over docetaxel was reasonable.

Economic analysis

- 6.20 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 PFS data of the CA209-017 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 8: 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.

- 6.21 The key drivers of the model are summarised below.

Table 9: 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 both arms, assuming continued treatment effect	High, favours nivolumab
Duration of nivolumab treatment	CA209-017 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 2-5 years and beyond 5 years were assumed to be halved and quartered respectively compared with the costs in the first 2 years.	Moderate, favours nivolumab
Utility value	CA209-017 trial-based utility data	Moderate, favours nivolumab
Ongoing disease management costs for pre-progression disease	The submission assumed that during pre-progression period, patients treated with nivolumab would require 80% of the costs of health care resources of those treated with docetaxel, based on one clinician's opinion.	Moderate, favours nivolumab

PFS=progression-free survival; OS=overall survival

Source: compiled during the evaluation.

- 6.22 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 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.2-3) 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 84 years of age, and that it was clinically plausible, primarily for the younger patients, to expect a proportion of this cohort to 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.
- 6.23 The submission used three methods to derive the time point from which to extrapolate the Kaplan-Meier OS and PFS curves of the CA209-017 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. However, the truncation time point of █ weeks, reported as the end of available trial-based Kaplan-Meier curve for OS in the docetaxel arm, appeared to be incorrect. The overall survival curves presented in the submission indicate that maximum duration of follow-up for OS in the docetaxel arm exceeds 30 months. It was unclear whether the exclusion of later data points in the docetaxel arm changed the extrapolated curve function.
- 6.24 The submission chose the log-logistic parametric distributions for extrapolation of both OS and PFS in both arms. The submission stated that these selections were based on both face validity and goodness of fit statistics. Visual inspection of the curves indicates that the extrapolation using log-logistic models is more optimistic than that using Weibull models in predicting OS and PFS for both treatment arms.

The model was sensitive to the methods of extrapolation. When using the Weibull model to extrapolate both PFS and OS in both arms, the incremental cost effectiveness ratio (ICER) increased to more than \$75,000/QALY-\$105,000/QALY gained. The PSCR (p.3) maintained that the log-logistic function was the most appropriate. The ESC noted that the Weibull function would be more conservative. The Pre-PBAC Response (p.2) acknowledged the sensitivity of the modelled economic evaluation to different parametric functions, however argued that “the log-logistic OS curve predicts 19% of patients will still be alive at 3 years, whereas the Weibull OS curve predicts 12% of patients will be alive at 3 years. Results from CA209-003, which reported data specific to squamous NSCLC patients demonstrated that 28% of patients are still alive at 3 years – thereby illustrating that application of both the log-logistic and Weibull functions may be conservative.”

- 6.25 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 horizon.
- 6.26 Utilities were derived from CA209-017. 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.
- 6.27 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, the submission assumed that, during the pre-progression period, patients treated with nivolumab would require 80% of the costs of health care resources of those treated with docetaxel, based on one clinician’s opinion, on the grounds of nivolumab’s better tolerability. 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. Compared with the model for non-squamous NSCLC, this assumption had a relatively large impact on the result of the economic evaluation for the treatment of squamous NSCLC, because the majority (about 80%) of survival gain of nivolumab compared with docetaxel was obtained from the progression-free state. The PSCR (p.4) argued that “applying 80% of the cost of the docetaxel arm to the nivolumab arm is not only reasonable given the improved tolerability of nivolumab compared with docetaxel, but potentially conservative.” The ESC considered that there was inadequate evidence to support this assertion.
- 6.28 The submission also 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 have a

longer post-progression survival than those treated with docetaxel, reducing costs for long-term survivors favoured the nivolumab arm. The PSCR (p.4-5) cited follow-up after cancer treatment fact-sheets to argue that patients require less frequent follow-up over time, however the ESC considered 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.

- 6.29 The mean durations of therapy, which were [redacted] infusions for nivolumab and [redacted] infusions for docetaxel, as observed in CA209-017, were used in the modelled economic evaluation. This was inappropriate and underestimated the costs of nivolumab and docetaxel. Given that health outcomes were 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 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 corresponding costs of treatment linked to those health outcomes.
- 6.30 Results of the economic evaluation are presented below.

Table 10: Results of the stepped economic evaluation

Step and component	Nivolumab	Docetaxel	Increment
Step 1 and Step 2: Within trial duration costs and outcomes			
Costs*	\$ [redacted]	\$ [redacted]	\$ [redacted]
LYs	1.12	0.73	0.39
QALYs	0.83	0.50	0.33
Incremental cost/LY gained			\$ [redacted]
Incremental cost/QALY gained			\$ [redacted]
Step 3: modelled evaluation (extrapolating health outcome to 10 years, without extrapolating drug costs)			
Costs*	\$ [redacted]	\$ [redacted]	\$ [redacted]
LYs	1.77	0.98	0.79
QALYs	1.30	0.66	0.63
Incremental cost/extra LY gained			\$ [redacted]
Incremental cost/extra QALY gained			\$ [redacted]

LY=life year; QALY=quality-adjusted life year
 * Drug costs are based on ex-manufacturer's prices.
 Source: Tables 74-77, pp163-4 of the submission.

- 6.31 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.
- 6.32 Extrapolating health outcomes to 10 years without extrapolating drug usage substantially decreased the ICER in favour of nivolumab.
- 6.33 The results of key sensitivity analyses are presented below.

Table 11: Results of key sensitivity analyses

Label	Model parameter	\$/LY	\$/QALY
Base case	Base case	\$ [redacted]	\$ [redacted]

Label	Model parameter	\$/LY	\$/QALY
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]
SA.5: Method of extrapolation	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]
	Respective trial-based nivolumab and docetaxel utility values*	\$ [REDACTED]	\$ [REDACTED]
SA.7: Ongoing disease management costs	Docetaxel and nivolumab pre-progression and post-progression costs equal (SA.7-1)	\$ [REDACTED]	\$ [REDACTED]
	Post-progression costs equal to that estimated from the HRU survey regardless of years spent in progressive disease (SA.7-2)	\$ [REDACTED]	\$ [REDACTED]
	SA.7-1+SA.7-2	\$ [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 for nivolumab	\$ [REDACTED]	\$ [REDACTED]
SA.8 + SA.9	5-year time horizon and including wastage of nivolumab (extrapolation methods used as in the base case – log-logistic model for both PFS and OS in both arms)	\$ [REDACTED]	\$ [REDACTED]
SA.7-1 + SA.7-2 + SA.8 + SA.9	5-year time horizon, including wastage of nivolumab, assuming docetaxel and nivolumab pre-progression and post-progression costs equal, and post-progression costs equal regardless of years spent in the progressive disease	\$ [REDACTED]	\$ [REDACTED]
SA.5 + SA.8 + SA.9	5-year time horizon, including wastage of nivolumab and extrapolation using Weibull for PFS and OS in both arms	\$ [REDACTED]	\$ [REDACTED]
SA.5 + SA.7-1 + SA.7-2 + SA.8 + SA.9	5-year time horizon, including wastage of nivolumab, assuming docetaxel and nivolumab pre-progression and post-progression costs equal, and post-progression costs equal regardless of years spent in progressive disease, extrapolating using Weibull model for both PFS and OS in both arms	\$ [REDACTED]	\$ [REDACTED]

* Since the observed utility for progressive disease in the nivolumab arm in CA2-09-017 was lower than that in the docetaxel arm, the observed utility value for “progressive disease” in the docetaxel treatment arm was applied to both treatment arms in the base case. The submission argued that “it seems implausible that patients in the nivolumab treatment arm should have a lower ‘progressive disease’ utility value”.

** Wastage of docetaxel was not included, but this would 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 79, p167 of the submission and additional analyses conducted during the evaluation.

- 6.34 Table 11 indicates that the model was sensitive to time horizon, treatment effect of nivolumab compared with docetaxel in terms of 95% confidence intervals for PFS and OS, method of extrapolation, utility values and the assumption that the disease management cost reduces substantially when patients survive more than 2 years post progression.
- 6.35 Time horizon and extrapolation methods had the most impact on the result of the economic evaluation. When using a 3-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 both PFS and OS with Weibull models in both treatment arms, the ICER increased to \$75,000/QALY - \$105,000/QALY gained.
- 6.36 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, while keeping the extrapolation method of log-logistic model as used in the base case. Additionally, when extrapolating PFS and OS using Weibull model for both arms, the ICER further increased to \$105,000/QALY - \$200,000/QALY gained.

- 6.37 When applying the estimated post-progression costs from HRU survey results to all post-progression years, the ICER increased to \$75,000/QALY - \$105,000/QALY gained. If further assuming pre-progression costs being equal in both arms, the ICER increased to \$75,000/QALY - \$105,000/QALY gained. The ICER would increase to more than \$105,000/QALY - \$200,000/QALY gained when also assuming a 5-year time horizon and including wastage of nivolumab, while keeping the extrapolation methods as that used in the base case.

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

- 6.38 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 74.25 kg for a patient, requiring 222.75 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 CA209-017 (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 \$ [REDACTED] for treatment with docetaxel, based on its usage in CA209-017.

Estimated PBS usage & financial implications

- 6.39 The submission was considered by DUSC. The submission took an epidemiological approach to estimate the number of patients with squamous NSCLC each year. The submission further estimated the proportion of patients treated with second- and third-line therapies based on expert opinion.
- 6.40 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.
- 6.41 The total cost of nivolumab was likely to be an underestimate since the treatment duration was assumed to be that observed in CA209-017. 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 squamous NSCLC are summarised below. The net cost to the PBS/RPBS over five years was estimated to be more than \$100 million.

Table 12: Estimated extent of nivolumab use and associated costs to the PBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Patients treated with nivolumab	█	█	█	█	█
Number of administrations ^a	█	█	█	█	█
Number of vials ^b 100mg/mL ^a 40mg/4mL (wastage included) ^a	█	█	█	█	█
Estimated drug cost to the PBS and RPBS					
Cost to the PBS/RPBS (including wastage) ^{a,b,c,d}	\$ █	\$ █	\$ █	\$ █	\$ █
Patient co-payments	\$ █	\$ █	\$ █	\$ █	\$ █
Net drug cost to the PBS/RPBS (including wastage) ^{a,b,c,d}	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated cost offsets					
Reduction in patients using docetaxel due to nivolumab	█	█	█	█	█
Net savings to PBS/RPBS ^d	\$ █	\$ █	\$ █	\$ █	\$ █
Overall cost to the PBS/RPBS					
Overall net cost ^{a,b,c,d}	\$ █	\$ █	\$ █	\$ █	\$ █

Source: Commentary on the main submission, Tables E.2.3 (p76), E.3.1 (p77) and E.4.1 (p78).

^a Assuming █ administrations per patient.

^b Assuming on average one patient needs 223.0mg of nivolumab with a body weight of 74.25kg. To supply 223.0mg of nivolumab, 2 vials of 100mg/10mL and 0.58 vials of 40mg/4ml were assumed in the submission. During the evaluation, 2 vials 100mg/mL and 1 vial 40mg/4mL were used in the sensitivity analysis.

^c 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.

^d Revised during the evaluation to include wastage. The dispensed prices of docetaxel were updated to include a 1.4% pharmacy mark- up for private hospitals and the preparation fee of \$102.67. Excludes patient copayments.

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

6.42 DUSC considered the estimates presented in the submission to be underestimated. The main issues were:

- The financial implications to government may be significantly underestimated by applying a ‘wider’ versus ‘narrower’ definition of NSCLC to estimate the squamous NSCLC eligible population (18.3% vs. 25.8%, 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 “increase in cost to the PBS for the squamous NSCLC indication is offset by a reduction in PBS cost for the non-squamous indication.”
- 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.
- The duration of nivolumab treatment in practice would likely be longer than the estimate based on Trial 017 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

- 6.43 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

- 6.44 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 negotiation 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 squamous NSCLC on the basis that acceptable cost-effectiveness 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 too high and likely to be significantly underestimated.
- 7.2 The PBAC recognised that there is a high clinical need for new treatments for patients with NSCLC, especially for the squamous histological subtype, 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 any 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;
 - no clear predictive effect of PD-L1 status on the comparative effectiveness of nivolumab was demonstrated in the pivotal clinical trial CA209-017, therefore it would be appropriate to allow treatment for patients regardless of PD-L1 status.

- 7.4 The PBAC considered that the submission's nominated comparator, docetaxel, was appropriate.
- 7.5 The PBAC 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. The PBAC noted that the mean age in trial CA209-017 was 62 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 populations would have implications for the estimation of comparative benefits and utilisation.
- 7.6 The PBAC considered that the claim of superior comparative effectiveness over docetaxel was reasonable, noting the incremental benefit in median overall survival of 3.2 months. The PBAC noted however, that the incremental benefit in median progression-free survival was 0.7 months.
- 7.7 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.
- 7.8 The PBAC considered that the claim of superior comparative safety over docetaxel was reasonable, noting the more favourable adverse event profile of nivolumab for Grade 3 and more drug-related adverse events and for neutropenia compared with docetaxel.
- 7.9 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 too 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 6.22) that a five-year time horizon would be more appropriate;
 - the method of extrapolation: sensitivity analysis using Weibull extrapolation increased the ICER to more than \$100,000 per QALY gained;
 - 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.
- 7.10 The PBAC noted that the estimated net cost of nivolumab for squamous NSCLC was more than \$████ 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.
- 7.11 The PBAC considered that any resubmission should be a major submission to allow for evaluation of an improved economic model.
- 7.12 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 squamous NSCLC.