

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

1 Purpose of Application

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

2 Requested listing

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

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

^a The dispensed prices for the maximum amount of 360 mg have been updated during the evaluation to include the indexation of fees for the efficient funding of chemotherapy drugs that occurred on 1st July 2016¹. The re-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:	Non-squamous non-small cell lung cancer
PBS Indication:	Locally advanced or metastatic non-squamous non-small cell lung cancer
Treatment phase:	Initial treatment

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

Public Summary Document – November 2016 PBAC Meeting

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

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

^a The dispensed prices for the maximum amount of 360 mg have been updated during the evaluation to include the indexation of fees for the efficient funding of chemotherapy drugs that occurred on 1st July 2016². The re-submission proposed a special pricing arrangement.

Category / Program	Section 100 – Efficient Funding of Chemotherapy
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Condition:	Non-squamous non-small cell lung cancer
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² Distribution fee \$25.92, diluent fee \$5.14, preparation fee \$103.22, ready prepared dispensing fee \$7.02.

Public Summary Document – November 2016 PBAC Meeting

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:	<p><i>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC</i></p> <p><i>AND</i></p> <p><i>Patient must have previously been issued with an authority prescription for this drug for this condition</i></p> <p><i>AND</i></p> <p><i>The treatment must be the sole PBS-subsidised therapy for this condition</i></p> <p><i>AND</i></p> <p><i>Patient must be deriving clinical benefit and tolerating treatment.</i></p> <p><i>Patient must have stable or responding disease.</i></p>
Administrative Advice:	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p> <p>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.</p>

2.2 The proposed restriction was broader than the TGA-approved indication for non-squamous NSCLC in not specifying that, in patients with tumour epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic aberrations, nivolumab should be used after progression on or after targeted therapy. The PSCR (p.2) agreed to the alignment of the PBS restriction with the TGA-approved indication for non-squamous NSCLC.

2.3 In contrast to the requested restriction in the original submission:

- The re-submission indicated that it was the intention for patients with "not otherwise specified (NOS)" NSCLC to be eligible for nivolumab under the non-squamous indication;
- The revised initial treatment restriction required patients to have a performance score of 0 or 1. This is consistent with the eligibility criteria in the key clinical trial for nivolumab (CA209-057); and
- The continuing treatment restriction contained a note acknowledging early "pseudo-progression" associated with immunotherapy with programmed cell death-1 (PD-1) inhibitors.

These changes were consistent with the PBAC considerations outlined in the Public Summary Document (PSD) for the original nivolumab submission (paragraph 7.3, 5.07 nivolumab PSD, March 2016 PBAC meeting).

2.4 In contrast to the restrictions for PD-1 inhibitors already listed on the PBS:

- The requested restriction for initial treatment did not preclude use of nivolumab in patients who have received prior treatment with a PD-1 inhibitor for the condition. The PSCR (p.1) indicated a willingness to ensure inclusion of specific wording

- relating to the use of multiple PD-L1 inhibitors.
 - The requested restriction for continuing treatment did not contain the criterion requiring stable or responding disease, which the PBAC previously stated would be necessary (paragraph 7.3, 5.07 nivolumab PSD, March 2016 PBAC Meeting). The PSCR (p.2) agreed to the inclusion of this criterion in the continuing restriction.
- 2.5 As in the original submission, the proposed listing did not restrict nivolumab to patients whose tumours express programmed death ligand-1 (PD-L1). The PBAC previously acknowledged the evidence for treatment effect variation by PD-L1 status in trial CA209-057. 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 (paragraphs 7.7 and 7.8, 5.07 nivolumab PSD, March 2016 PBAC meeting).
- 2.6 The PBAC noted that, 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 (paragraph 7.3, 5.07 nivolumab PSD, March 2016 PBAC Meeting).
- 2.7 The re-submission sought listing on the basis of a cost-effectiveness analysis via a direct comparison with docetaxel and an indirect comparison with pemetrexed.

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

3 Background

- 3.1 Nivolumab was registered on the Australian Register of Therapeutic Goods on 18 February 2016 for the following indication relevant to this re-submission:
Nivolumab, as monotherapy, is indicated for the treatment of locally advanced or metastatic non-squamous NSCLC with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, nivolumab should be used after progression on or after targeted therapy.
- 3.2 This was the second submission to the PBAC for the requested listing. A previous submission was considered at the March 2016 PBAC meeting.
- 3.3 The PBAC also considered a concurrent re-submission to list nivolumab for squamous NSCLC at its November 2016 meeting.
- 3.4 As noted earlier, the requested listing was broader than the approved TGA indication in not specifying that, in EGFR or ALK positive patients, nivolumab should only be used after progression on targeted therapy.
- 3.5 In comparison with the original submission, the re-submission included pemetrexed as an alternative main comparator and conducted a cost-utility analysis on the basis of an indirect comparison of nivolumab versus pemetrexed. The re-submission also updated some model inputs in response to PBAC's concerns on the original submission.

4 Clinical place for the proposed therapy

- 4.1 NSCLC comprises approximately 15%-25% of the squamous histologic subtype and 75%-85% of the non-squamous histologic subtype. In current practice, approximately 20% of patients would receive tyrosine kinase inhibitors (TKIs) first-line (targeting EGFR gene mutations or ALK translocations), followed by platinum-based chemotherapy upon progression, and subsequent pemetrexed or docetaxel. Patients with no EGFR or ALK mutations/translocations would initiate treatment with platinum-based chemotherapy, and subsequently receive pemetrexed or docetaxel.
- 4.2 The proposed listing was for patients with non-squamous NSCLC who have failed platinum-based chemotherapy. Thus, nivolumab would displace pemetrexed and docetaxel to further down the treatment pathway.
- 4.3 The intended place for nivolumab in the treatment of non-squamous NSCLC was unchanged from the previous submission.

5 Comparator

- 5.1 The re-submission nominated both docetaxel and pemetrexed as the main comparators. In the original submission, docetaxel was nominated as the main comparator and pemetrexed as a minor comparator. The PBAC previously considered that, for non-squamous NSCLC, pemetrexed was the main comparator (paragraph 7.4, 5.07 nivolumab PSD, March 2016 PBAC Meeting).

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

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (5), health care professionals (11) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the value of nivolumab as another treatment option for non-squamous NSCLC, including the clinically meaningful outcomes for patients and good tolerability of the drug in comparison to docetaxel.
- 6.3 The PBAC noted the input received from the Medical Oncology Group of Australia (MOGA) and the Lung Foundation of Australia, both providing strong support for nivolumab. The input from MOGA highlighted the high clinical value of nivolumab in

squamous NSCLC, citing a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) evaluation score for non-curative therapies of 4 in comparison to docetaxel (where 5 and 4 represent the grades with substantial improvement)³.

Clinical trials

- 6.4 The re-submission was based on one head-to-head trial (CA209-057) comparing nivolumab (3 mg/kg every two weeks) to docetaxel (75 mg/m² every three weeks) in previously treated patients with metastatic non-squamous NSCLC (N=582). An indirect comparison with pemetrexed, using docetaxel as the common reference, was also conducted, based on CA209-057 and a retrospective analysis of the non-squamous subgroup (Scagliotti (2009): N=399) from a trial which compared pemetrexed with docetaxel in NSCLC (Hanna et al (2004): N=571).
- 6.5 Details of the trials presented in the re-submission are provided in the table below. These trials were unchanged from the previous submission. Updated data from the trial CA209-057 was provided. An indirect comparison of nivolumab versus pemetrexed using CA209-057 and Scagliotti (2009) was presented as supportive evidence in the previous submission, without providing an economic analysis. In response to the PBAC's judgement that pemetrexed was the main comparator for non-squamous NSCLC, the re-submission presented the indirect comparison as an additional set of key evidence and included an economic evaluation of nivolumab versus pemetrexed.

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

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

Trial ID	Protocol title/ Publication title	Publication citation
Common reference of docetaxel		
Proposed drug: Nivolumab		
CA209-057	<p>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) – (based on database lock March 2015).</p> <p>Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer.</p> <p><u>Abstract</u></p> <p>Horn L., Brahmer J, et al. Phase 3, randomized trial (CheckMate 057) of nivolumab (NIVO) vs docetaxel (DOC) in advanced non-squamous (non-SQ) non-small cell lung cancer (NSCLC) : subgroup analyses and patient reported outcomes (PROs).</p> <p><u>Poster presentation</u></p> <p>Borghaei H, Brahmer J, Horn L, et al. Nivolumab vs docetaxel in patients with advanced NSCLC: CheckMate 017/057 2-year update and exploratory cytokine profile analyses.</p>	<p>May 2015</p> <p>New England Journal of Medicine 2015; 373:1627-39</p> <p>European Journal of Cancer 2015; 51:S599 (Abstract)</p> <p>American Society of Clinical Oncology 2016 Annual Meeting; June 3-7, 2016; Chicago, Ill., USA.</p>
Comparator: Pemetrexed		
Hanna (2004)	Hanna N, Shepherd FA, Fossella FV et al. Randomised phase III trial of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy.	Journal of Clinical Oncology 2004; 22 (9): 1589-1597.
Scagliotti (2009)	Scagliotti G, Hanna, N, Fossella, F et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies.	The Oncologist 2009; 14: 253-263.

Source: Table 12, p40 and Table 21, pp58-60 of the re-submission.

- 6.6 The key features of the direct randomised trial and studies used in the indirect comparison 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 75 mg/m² Q3W						
CA209-057	582	R, OL Database lock March 2015 (follow-up 13.2 months), Database lock July 2015 (follow-up 17.1 months); Database lock February 2016 (follow-up 24 months)	Low for OS High for AEs and QoL.	Stage IIIB/Stage IV non-squamous NSCLC patients who had failed platinum-based chemotherapy	Overall survival	Used
Pemetrexed 500 mg/m² Q3W vs docetaxel 75 mg/m² Q3W.						
Scagliotti (2009)	399	Post hoc subgroup analysis of non-squamous patients from Hanna (2004) (N=571)	High	Stage IIIB/Stage IV non-squamous NSCLC Patients who have received one prior chemotherapy regimen (except pemetrexed or docetaxel)	Overall survival	Used
Nivolumab versus pemetrexed						
Indirect comparison of CA209-057 with Scagliotti (2009)			High	As above	Overall survival	Used

AEs=adverse events; NSCLC = non-small cell lung cancer; OL=open label; OS=overall survival; Q2W=every 2 weeks; Q3W=every 3 weeks; QoL=quality of life; R=randomised
Source: compiled during the evaluation.

- 6.7 The comparison of nivolumab versus docetaxel was based on the key trial CA209-057. This was unchanged from the previous submission. This trial was also used in the indirect comparison of nivolumab and pemetrexed. The updated overall survival (OS) and safety results have been presented below.
- 6.8 As in the original submission, the re-submission presented an indirect comparison of nivolumab and pemetrexed, with docetaxel as the common comparator, based on the following clinical evidence:
- CA209-057: An open-label randomised controlled trial (RCT) comparing nivolumab with docetaxel in previously treated metastatic non-squamous NSCLC (N=582); and
 - Scagliotti (2009): A retrospective analysis of the non-squamous subgroup of patients (N=399) from an RCT comparing pemetrexed with docetaxel in patients with NSCLC (Hanna (2004): N=571).
- 6.9 The limited baseline data reported for both the intention-to-treat (ITT) population and the non-squamous subgroup in Hanna (2004) made it difficult to fully assess the transitivity of the two sources of trial results for the indirect comparison. However, a comparison of the available data suggested that the trial populations differed in respect to a number of potential prognostic factors and treatment effect modifiers, including: gender balance, race, disease stage, histology subtype, the inclusion of patients with Eastern Cooperative Oncology Group (ECOG) performance status 2 in Hanna (2009) and the inclusion of patients receiving third-line therapy in CA209-057. The proportion of patients who received further systemic cancer therapy after discontinuing docetaxel also varied substantially across the common docetaxel

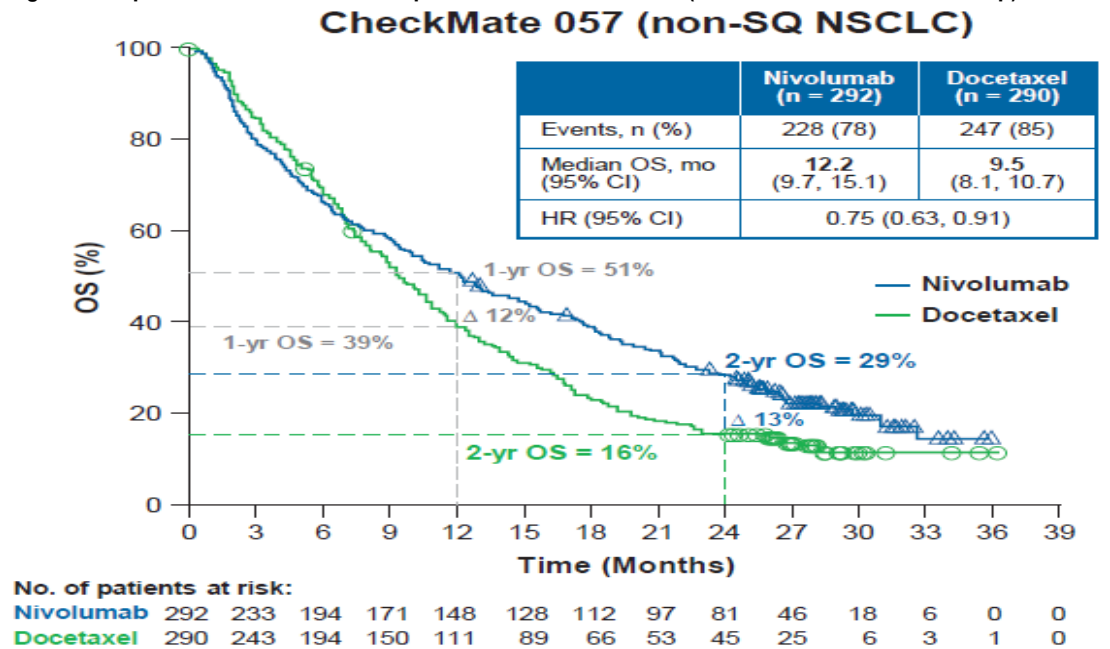
reference arms. There was considerable potential for confounding in the indirect comparison of outcomes between the trials.

Comparative effectiveness

Nivolumab versus docetaxel

6.10 The Kaplan-Meier curves for OS, based on the updated results from trial CA209-057 (24 months minimum follow-up), are presented below in Figure 1.

Figure 1: Kaplan-Meier overall survival plot – ITT Trial CA209-057 (24 months minimum follow-up)



CI = confidence interval; HR = hazard ratio; non-SQ NSCLC = non-squamous non-small cell lung cancer; OS = overall survival
Source: Figure 4, p42 of the re-submission.

6.11 Table 3 compares the updated OS results, based on the 24 months minimum follow-up data, with those presented in the original submission (17.1 months minimum follow-up).

Table 3: Overall survival results from Trial CA209-057

Source	Borghaei et al (2015) Database lock July 2015		Borghaei et al (2016) Database lock February 2016	
	17.1 months		24 months	
Minimum follow-up	Nivolumab N=292	Docetaxel N=290	Nivolumab N=292	Docetaxel N=290
Number of events, n (%)	206 (70.5)	236 (80.8)	228 (78.1)	247 (85.2)
Median, months (95% CI)	12.2 (9.7, 15.1)	9.4 (8.1, 10.7)	12.2 (9.7, 15.1)	9.5 (8.1, 10.7)
	Nivolumab vs docetaxel		Nivolumab vs docetaxel	
Stratified HR (95% CI)	0.72 (0.60, 0.88)*		0.75 (0.63, 0.91)*	
Stratified log-rank	p = 0.0009		NR	

CI = confidence interval; HR = hazard ratio; NR = not reported.

* Proportional hazards assumption was not met

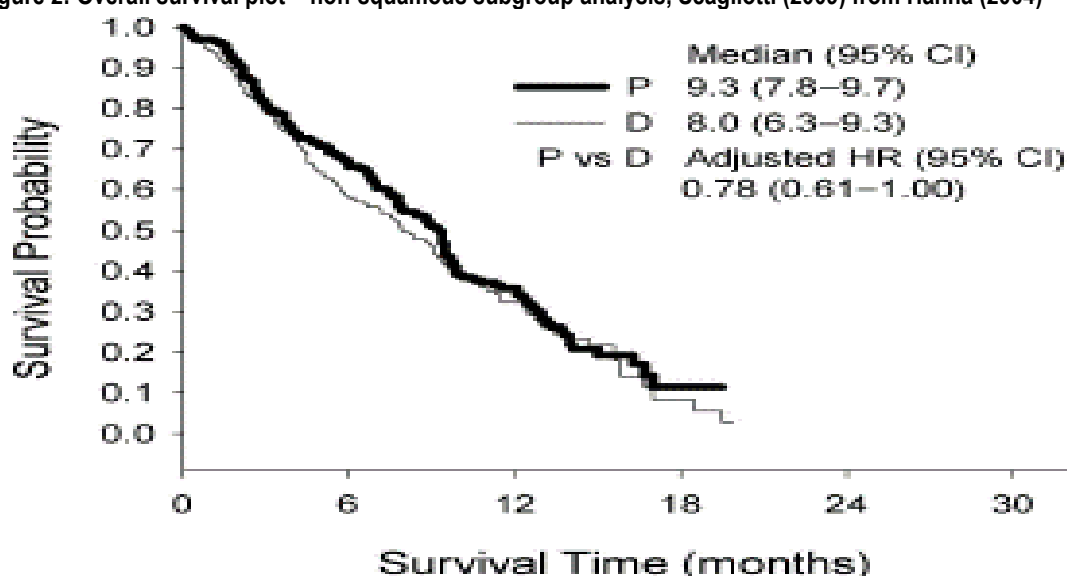
Source: Table 13, p43 of the re-submission.

- 6.12 The updated results were similar to those presented in the original submission and did not alter any of the previous conclusions regarding the comparative effectiveness of nivolumab versus docetaxel in patients with non-squamous NSCLC.
- 6.13 In regard to the OS results for CA209-057, the PBAC previously 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 (HR), 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 (paragraph 7.6, 5.07 nivolumab PSD, March 2016 PBAC Meeting).
- 6.14 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 (paragraph 7.7, 5.07 nivolumab PSD, March 2016 PBAC Meeting).

Pemetrexed versus docetaxel

- 6.15 The Kaplan-Meier curves for OS, for the subgroup of patients with non-squamous NSCLC in Scagliotti (2009), are presented in Figure 2.

Figure 2: Overall survival plot – non-squamous subgroup analysis, Scagliotti (2009) from Hanna (2004)



CI = confidence interval; D = docetaxel; HR = hazard ratio; P = pemetrexed
 Source: Figure 9, p70 of the re-submission.

Indirect comparison of nivolumab and pemetrexed (non-squamous NSCLC)

- 6.16 Table 4 below summarises the results of the indirect comparison of OS for nivolumab versus pemetrexed in patients with non-squamous NSCLC, based on data from the extended follow-up CA209-057 database lock (24 months minimum follow-up).

Table 4: Overall survival - Indirect comparison of nivolumab vs pemetrexed in patients with non-squamous NSCLC (CA209-057 minimum follow-up 24 months)

	Nivolumab CA209-057 ^a		Pemetrexed trial Scagliotti (2009) ^b		Indirect treatment effect nivolumab vs pemetrexed
	Nivolumab	Docetaxel	Pemetrexed	Docetaxel	
N	292	290	205	194	0.96 (0.71, 1.31)
Number of events, n (%)	228 (78.1)	247 (85.2)	NR	NR	
Median, months (95% CI)	12.2 (9.7, 15.1)	9.4 (8.1, 10.7)	9.3 (7.8, 9.7)	8.0 (6.3, 9.3)	
HR (95% CI)	0.75 (0.63, 0.91)		0.78 (0.61, 1.00)		

CI = confidence interval; HR = hazard ratio; NSCLC = non-small cell lung cancer; NR = not reported

^a Database lock February 2016 (24 months minimum follow-up)

^b Retrospective analysis of non-squamous subgroup from Hanna (2004).

Figures in italics were calculated during the evaluation. The re-submission presented the indirect comparison based on the 17.1 months minimum follow-up results from CA209-057, which gave an indirect HR for nivolumab vs pemetrexed of 0.92 (95% CI: 0.68, 1.26).

Source: Table 13, p43 and Table 26, p72 of the re-submission; Figure 2, p259 Scagliotti (2009).

- 6.17 Given the considerable transitivity issues across the trials, the fact that the HR from trial CA209-057 was not a reliable measure of the relative treatment effect of nivolumab versus docetaxel, and the reliance on a retrospective analysis of the non-squamous NSCLC subgroup from Hanna (2004), the validity of the indirect comparison was highly uncertain and the results should be interpreted with caution.

Comparative harms

- 6.18 Table 5 summarises the updated safety data (minimum follow-up of 24 months) for nivolumab compared with docetaxel in CA209-057.

Table 5: CA209-057 Summary of treatment-related AEs (24 months minimum follow-up)

	Nivolumab n (%) N=287	Docetaxel n (%) N=268	Relative risk (95% CI)	Risk difference (95%CI)
Treatment related AEs				
Any grade	204 (71)	236 (88)	0.81 (0.74, 0.88)	-0.17 (-0.24, -0.10)
Grade 3-4	32 (11)	145 (54)	0.21 (0.15, 0.29)	-0.43 (-0.50, -0.36)
Treatment-related AE leading to discontinuation				
Any grade	17 (6)	40 (15)	0.40 (0.23, 0.68)	-0.09 (-0.14, -0.04)
Grade 3-4	11 (4)	19 (7)	0.54 (0.26, 1.11)	-0.03 (-0.07, 0.01)
Treatment-related deaths	1 (<1) ^a	1 (<1) ^a	-	-
Most frequent treatment-related AEs of any grade (≥10% of patients)				
Fatigue	49 (17)	78 (29)	0.59 (0.43, 0.80)	-0.12 (-0.19, -0.05)
Nausea	34 (12)	70 (26)	0.45 (0.31, 0.66)	-0.14 (-0.21, -0.08)
Decreased appetite	32 (11)	43 (16)	0.69 (0.45, 1.06)	-0.05 (-0.11, 0.01)
Asthenia	29 (10)	48 (18)	0.56 (0.37, 0.87)	-0.08 (-0.14, -0.02)
Diarrhoea	26 (9)	62 (23)	0.39 (0.26, 0.60)	-0.14 (-0.20, -0.08)
Anaemia	6 (2)	53 (20) ^b	0.11 (0.05, 0.24)	-0.18 (-0.23, -0.13)
Neutropenia	1 (0.3)	83 (31)	0.01 (0.00, 0.08)	-0.31 (-0.36, -0.25)
Alopecia	1 (0.3)	67 (25)	0.01 (0.00, 0.10)	-0.25 (-0.30, -0.19)
Myalgia	6 (2)	29 (11)	0.19 (0.08, 0.46)	-0.09 (-0.13, -0.05)
Peripheral oedema	9 (3)	27 (10)	0.31 (0.15, 0.65)	-0.07 (-0.11, -0.03)
Febrile neutropenia	0	27 (10)	0.00	0.00
Leukopenia	0	27 (10)	0.00	0.00

AE = adverse event; CI = confidence interval

^a One death from encephalitis in the nivolumab arm and one death reported as grade 4 febrile neutropenia in the docetaxel arm.

^bSource: Borghaei et al (2016). Reported as 27 (10%) in Table 15 of the re-submission.

Bolded figures indicate statistically significant difference

Source: Tables 14 and 15, p45 of the re-submission

- 6.19 Between the one- and two-year data cut-offs, two patients discontinued from nivolumab due to pemphigoid and rash. The association of one death for nivolumab (from encephalitis) was changed from 'not related to treatment' to 'treatment-related' after the one-year database lock. The updated two-year safety data were, otherwise, similar to those presented in the original submission. These data need to be interpreted in the context of the open-label design of the CA209-057 trial.
- 6.20 In regard to the original submission, the PBAC considered that the claim of superior comparative safety of nivolumab over docetaxel was reasonable; however, the PBAC also noted that nivolumab was associated with a significantly higher proportion of patients with Grade 3 and 4 endocrine adverse events (AEs) than docetaxel (paragraph 7.9, 5.07 nivolumab PSD, March 2016 PBAC Meeting).
- 6.21 For the indirect comparison of safety between nivolumab and pemetrexed, the rates of AEs in the docetaxel arms of CA209-057 and Hanna (2004) differed considerably, indicating poor exchangeability for indirect comparisons of safety outcomes. In addition, as Hanna (2004) did not report the incidence of some AEs known to be associated with nivolumab therapy (e.g. immune-mediated AEs, including endocrine AEs), a full comparison of the safety profile of nivolumab and pemetrexed was not possible.

- 6.22 On the basis of the limited information available, the re-submission claimed that the indirect comparison indicated that nivolumab was at least non-inferior in terms of safety to pemetrexed, and might be superior, as fatigue and nausea (of any grade) may occur at a significantly lower frequency with nivolumab than pemetrexed. The validity of the results remained highly uncertain given the poor exchangeability of the trials.
- 6.23 The risk of serious immune-related AEs associated with nivolumab may be higher in clinical practice than in a clinical trial setting where there is likely to be a heightened awareness and recognition of immune-related AEs, resulting in early intervention before such events progress to a more severe grade.
- 6.24 On 12 August 2015, the nivolumab Company Core Data Sheet was updated with a new warning for immune-related rash, including fatal toxic epidermal necrolysis, and encephalitis, based on cases identified during routine pharmacovigilance signal detection activities. The ESC previously noted that the AE 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 US Food and Drug Administration (paragraph 6.18, 5.07 nivolumab PSD, March 2016 PBAC Meeting).

Benefits/harms

- 6.25 As the updated results from the February 2016 database lock were similar to the results from the previous database locks, the benefits/harms of nivolumab and docetaxel were unchanged from the evaluation of the original submission.
- 6.26 The following summary of benefits and harms for nivolumab versus docetaxel is reproduced from the PBAC's March 2016 consideration:
- 6.27 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.
- 6.28 The comparative benefits for nivolumab versus pemetrexed, via an indirect comparison, were unable to be determined due to the uncertainty associated with the indirect comparison and the lack of information reported in Scagliotti (2009).

Clinical claim

Direct comparison of nivolumab and docetaxel

- 6.29 The PBAC previously accepted the claim of superior comparative effectiveness and superior comparative safety of nivolumab over docetaxel for the treatment of locally advanced or metastatic non-squamous NSCLC (paragraphs 7.6 and 7.9, 5.07 nivolumab PSD, March 2016 PBAC Meeting).

Indirect comparison of nivolumab and pemetrexed

- 6.30 The re-submission described nivolumab as superior in terms of comparative effectiveness and comparable in terms of comparative safety over pemetrexed in the treatment of Stage IIIB/Stage IV non-squamous NSCLC after progression on or after platinum-based chemotherapy.
- 6.31 The re-submission's claims were not adequately supported. No conclusive clinical claim can be made regarding the comparative effectiveness and safety of nivolumab over pemetrexed for the treatment of non-squamous NSCLC, given that:
- The indirect comparison failed to demonstrate any statistically significant difference in OS between nivolumab and pemetrexed;
 - The validity of the indirect comparison of both effectiveness and safety outcomes was highly uncertain:
 - There were considerable differences between CA209-057 and Hanna (2004) in terms of factors that were likely to confound the indirect comparison;
 - Due to violation of the proportional hazards assumption, the HR for OS from trial CA209-057 was not a reliable measure of the relative treatment effect of nivolumab versus docetaxel;
 - The estimated relative treatment effect of pemetrexed versus docetaxel in patients with non-squamous NSCLC was based on a post hoc subgroup analysis, with no stratification of randomisation by histology subtype; and
 - As Hanna (2004) only reported limited safety data, a full comparison of the safety profile of nivolumab and pemetrexed was not possible.
- 6.32 The re-submission further justified the clinical claim on the basis that the PBAC previously determined that:
- Pemetrexed is non-inferior when compared to docetaxel in the second-line treatment of NSCLC, and
 - Nivolumab displays superior efficacy and safety when compared to docetaxel in the second-line treatment of NSCLC.
- 6.33 The re-submission's justification was not reasonable. The PBAC's November 2004 decision to recommend listing of pemetrexed, on a cost-minimisations basis compared with docetaxel, was based on a population which included patients with both squamous and non-squamous NSCLC, and was made prior to the awareness that the effectiveness of pemetrexed differed according to NSCLC histology.
- 6.34 The PBAC considered that a claim of superior comparative effectiveness over pemetrexed was not well supported by the indirect comparison presented in the resubmission. However, the PBAC considered it likely that nivolumab provides an incremental clinical benefit compared with pemetrexed, also noting that the

Committee had previously accepted the claim of superior comparative effectiveness over docetaxel (although this claim was strongest in patients who are PD-L1 positive).

- 6.35 The PBAC noted that there was insufficient data to form a full comparison of the safety profiles of nivolumab and pemetrexed, however recalled that it had previously accepted a claim of superior comparative safety over docetaxel.

Economic analysis

- 6.36 The economic evaluation was a Markov model with three health states – progression-free, post-progression and death. The model structure was unchanged from the previous submission, apart from the time horizon being reduced to 7.5 years from 10 years. In response to the PBAC’s concern that pemetrexed was the main comparator for non-squamous NSCLC, the re-submission included an additional cost-utility analysis of nivolumab compared with pemetrexed on the basis of the indirect comparison. There were substantial uncertainties associated with the indirect comparison. The model structure and rationale are presented in the table below.

Table 6: Summary of model structure and rationale

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

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

Source: Table compiled during the evaluation

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

Table 7: Key drivers of the model

Description	Method/Value	Impact
Time point of extrapolation	Median time to censoring	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 until Year 5.	High, favours nivolumab
Assumed treatment effect of pemetrexed	The re-submission assumed that the survival benefit associated with pemetrexed was the same as that of docetaxel before the point for extrapolation, but applying HRs of 0.78 for OS and 0.82 for PFS to respective docetaxel survival curves to estimate the survival for pemetrexed after the extrapolation point.	High, favours nivolumab
Duration of nivolumab treatment	CA209-057 mean trial-based treatment duration – i.e. truncated with respect to resource use.	Moderate, favours nivolumab
Time horizon	7.5 years; assumed from 18-month trial results.	Moderate, favours nivolumab
Ongoing disease management costs for pre-progression disease	The re-submission assumed that during the pre-progression period, patients treated with nivolumab would require 60% of the disease management costs of those treated with docetaxel, based on a survey of the sponsor's Advisory Board members.	Moderate, favours nivolumab

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

- 6.38 The ESC considered that, as the modelled economic evaluation against pemetrexed was predicated on the unsupported assumption of superior efficacy of nivolumab over pemetrexed (rather than the actual results of the highly uncertain indirect comparison that suggested similar efficacy), the model is likely to be invalid, and cost-minimisation against pemetrexed would have been a more conservative approach.
- 6.39 The July 2016 price of pemetrexed was used in the economic evaluation. The pemetrexed price would be reduced following the impact of the next price disclosure cycle (in April 2017)⁴. This would be expected to have economic implications for nivolumab treatment of non-squamous NSCLC.
- 6.40 Although the updated survival results from the February 2016 database lock in CA209-057 (24 months minimum follow-up) were provided in the re-submission, they were not used in the revised economic evaluation. Instead, the survival data from an earlier database lock (July 2015) were applied to the model, unchanged from the economic evaluation in the original submission. The PSCR (p.4) provided results of the modelled economic analysis using the updated trial data at the February 2016 database lock. The ESC noted that using survival data from the extended follow-up database lock had minimal effect on the ICER when the log-logistic extrapolation was applied, but noted that PSCR did not use these extended data to either re-examine the basis for selecting between the log-logistic and Weibull based extrapolations, or present the Weibull-based ICER with extended data.
- 6.41 As in the original submission, the re-submission used three methods to derive the time point from which to extrapolate the Kaplan-Meier OS and progression-free

⁴ <http://www.pbs.gov.au/info/industry/pricing/price-disclosure-spd/drugs-subject-to-price-disclosure>

survival (PFS) curves for the comparative arms. In the base case of the model, the re-submission used median time to censoring based on the reverse Kaplan-Meier methodology (in which censoring was an endpoint and death was considered as a censored observation (Schemper and Smith 1996, provided in the re-submission)). Median duration of follow-up (i.e. median time trial subjects were observed in CA209-057) and the end of available Kaplan-Meier curves were used in sensitivity analyses. The ESC considered that this method is not reliable when substantially different patterns of censoring (such as frequency, intensity and quality of follow-up over the observation period) occur across the comparison, as in this case across the indirect comparison.

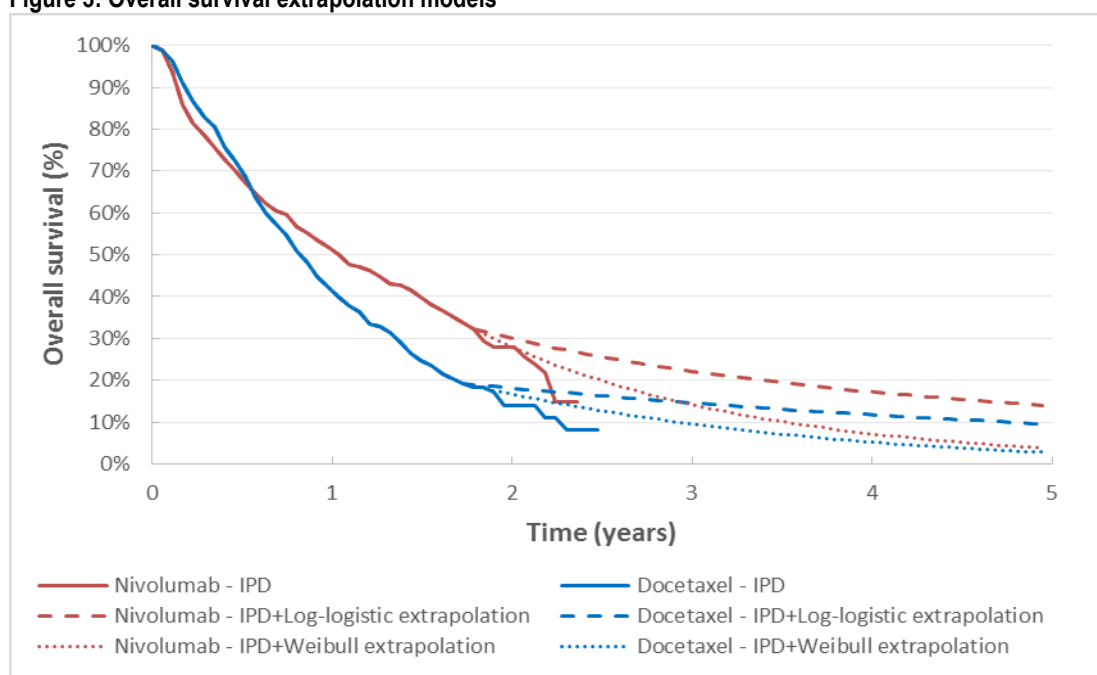
6.42 The assumption that, after the point of extrapolation, the PFS and OS curves would follow the chosen parametric functions continually until Year 5. In the absence of robust long-term survival data from patients treated with nivolumab, the ESC considered that this was not a reasonable assumption. Although the submission assumed a convergence of survival curves from Year 5 to Year 7.5, a convergence at such a late time point beyond the trial duration was not justified for the proposed population.

6.43 As in the original submission, the re-submission chose log-logistic parametric distributions for extrapolation of both OS and PFS of nivolumab, a log-logistic model for docetaxel PFS and a Weibull parametric distribution for docetaxel OS. The PBAC considered that the selection of parametric functions inappropriately overestimated the increments for both PFS and OS (nivolumab vs docetaxel) (paragraph 7.11, 5.07 nivolumab PSD, March 2016 PBAC meeting). The PSCR (p.3) asserted that the log-logistic method of extrapolation is a more appropriate method of long-term extrapolation for immunotherapy agents than the Weibull distributions, due to the following reasons:

- visual inspection of the curves indicate that log-logistic curves are of better fit for nivolumab PFS, OS and docetaxel PFS curves than the Weibull curves. The ESC disagreed with this observation, especially with regard to the OS curves (see Figure 3) and noted that a similar graph of curves for the extended follow-up to the February 2016 database lock had not been presented.
- the AIC for both nivolumab and docetaxel OS log-logistic curves indicate that they are more appropriate to use than Weibull curves, and vice versa for docetaxel OS Weibull curves. The ESC noted that the reported AICs could not be located in the resubmission and were also not reported for the extended follow-up to the February 2016 database lock.
- long-term data available for OS in CA209-003 is better represented by the log-logistic curves than Weibull curves.
- the Weibull distribution does not allow for non-zero hazards, contrary to the sharp initial decline observed for immune-oncology agents. The ESC considered that the purpose of adopting a curve of best fit against the available evidence is to project these curves beyond the available evidence to inform the extrapolation. Accordingly less weight should be given to the early shape of the curve representing the sharp initial decline.

The ESC maintained its previous view that the Weibull model function would be the preferred method of extrapolation for both treatment arms.

Figure 3: Overall survival extrapolation models



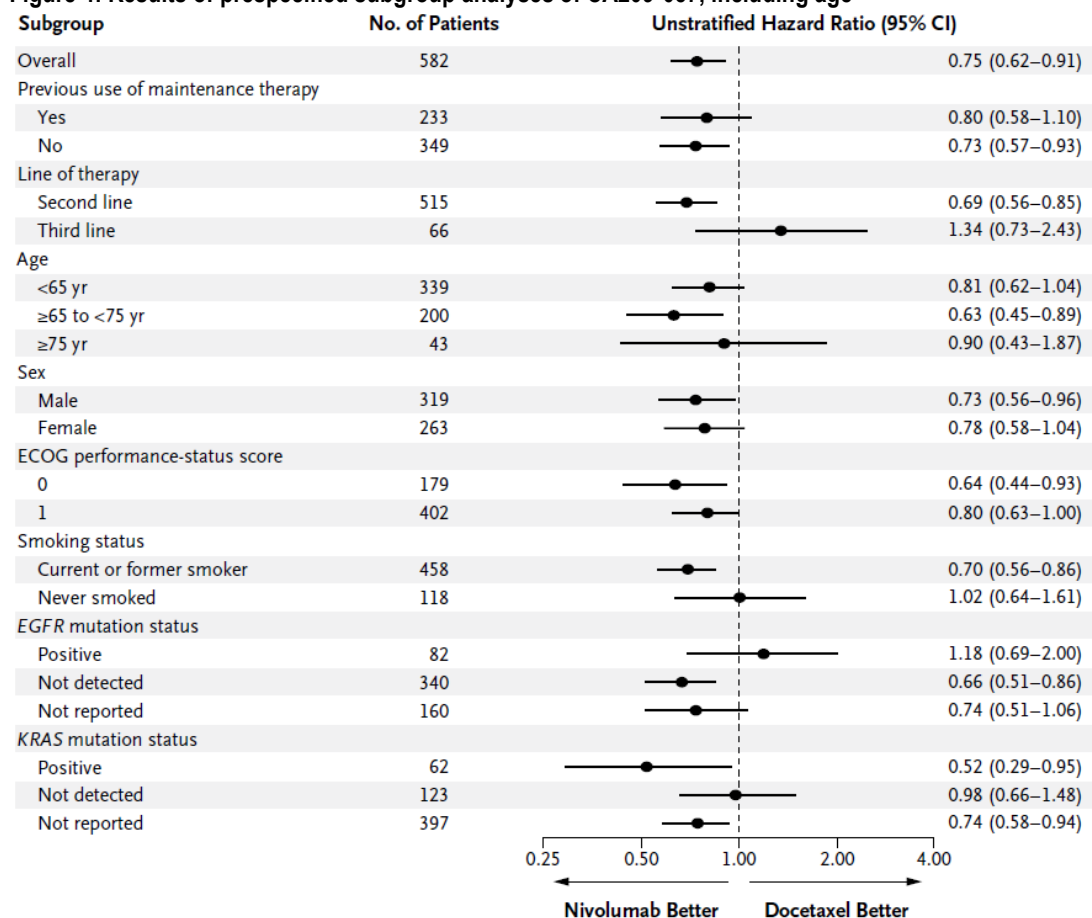
IPD = individual patient data

Note: IPD from trial CA209-057 at the July 2015 database lock (17.1 months minimum follow-up)

Source: Graph constructed during the evaluation (Figure C.2.2.2 of the Commentary)

- 6.44 In the re-submission, the survival estimates for patients in the pemetrexed arm were assumed to be identical to those of CA209-057 subjects who received docetaxel before the extrapolation point; after this time point, HRs of 0.78 for OS and 0.82 for PFS as reported in Scagliotti (2009) were applied to respective docetaxel extrapolated survival curves to estimate the survival for pemetrexed. The re-submission’s assumption of equivalent survival benefits (i.e. a HR of 1.00) between pemetrexed and docetaxel before the truncation point, but a more favourable PFS and OS for pemetrexed over docetaxel during extrapolation is not biologically plausible; nor has it been supported by any clinical evidence.
- 6.45 A time horizon of 7.5 years was used in the base case of the model, in comparison with a 10-year time horizon in the original submission. The PBAC considered that a 5-year time horizon was more appropriate (paragraph 7.11, 5.07 nivolumab PSD, March 2016 PBAC meeting). The PSCR (p.3) argued that the data provided in the resubmission supported use of a longer time horizon and that the resubmission “had already reduced the time horizon from 10 years to 7.5 with convergence in an attempt to meet the PBAC halfway”. At its March 2016 meeting, the PBAC noted that the age of the trial population may not be representative of the eligible Australian population, which was likely to be older, and therefore the extent of overall survival gain would be less (see Figure 4). The ESC considered that this would also suggest that 5 years was a more appropriate time horizon.

Figure 4: Results of prespecified subgroup analyses of CA209-057, including age



Source: Figure 2 of Borghaei H, et al. New England Journal of Medicine 2015; 373:1627-39.

- 6.46 The ESC advised that if the Weibull extrapolation was used, it would likely mitigate some of the issues regarding the time horizon as the curves converge at around 5 years.
- 6.47 The re-submission updated the average duration of therapy for nivolumab, which was ██████ infusions, based on the 2-year minimum follow-up data of CA209-057. At the 2-year analysis in CA209-057, 9.4% (27/287) of subjects were continuing nivolumab treatment compared to 0% (0/268) in the docetaxel arm. Given that the model extrapolated health outcomes beyond the trial period, the treatment duration for nivolumab should have been extrapolated correspondingly. Using trial-based (i.e. truncated) treatment durations underestimated the costs of nivolumab, but not of docetaxel, and biased the results of economic evaluation in favour of nivolumab. The ESC considered, as previously, that if the model extrapolates health outcomes to the end of the time horizon, then it should also extrapolate the corresponding costs of treatment linked to those health outcomes.
- 6.48 The re-submission assumed that patients treated with nivolumab would require 60% of the health care resources of those treated with docetaxel and pemetrexed, based on opinions from eight members of the sponsor’s Advisory Board. The representativeness of the expert opinion was uncertain. The re-submission’s assumption might have favoured nivolumab. The previous submission assumed that

patients treated with nivolumab would require 80% of the health care resources of those treated with docetaxel. The PSCR (p.4) asserted that the Advisory Board is a representative sample of clinicians and this assumption is reasonable, however the ESC did not agree that this was adequately justified. Further, the ESC considered that not all pre-progression costs related to adverse events and that it was therefore inappropriate to assume that the other health resource costs would reduce by the same proportion as the costs for management of adverse events.

- 6.49 The results of economic evaluation were revised during the evaluation by correcting a few miscalculations in the re-submission and incorporating the updated Efficient Funding of Chemotherapy (EFC) fees. The revised results of economic evaluation are summarised below.

Table 8: Revised results of economic evaluation – nivolumab vs pemetrexed^a

	Nivolumab	Pemetrexed	Increment
Economic evaluation within trial duration^b			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	1.184	1.030	0.154
QALYs	0.895	0.775	0.121
Incremental cost/LY gained			\$ [REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
Modelled economic evaluation (extrapolation to 7.5 years)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	1.786	1.279	0.507
QALYs	1.346	0.959	0.387
Incremental cost/LY gained			\$ [REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]

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

^a Results of economic evaluation were revised by: 1) correcting the re-submission's calculation of the survival estimates for pemetrexed after the extrapolation point via applying hazard ratios for pemetrexed versus docetaxel to the docetaxel hazard function from the survival curves; 2) correcting the re-submission's referencing errors while calculating the cumulative costs in the pemetrexed arm; and 3) taking into account the EFC fees.

^b No extrapolation but quality of life data and the cost of disease management (both pre- and post-progression) have been included.

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

The redacted table above shows that the incremental cost of nivolumab vs pemetrexed for the trial duration was \$75,000 - \$105,000 per LY gained and \$105,000 - \$200,000 per QALY gained, and when extrapolated to 7.5 years, was \$45,000 - \$75,000 per LY gained and \$45,000 - \$75,000 per QALY gained.

Table 9: Revised results of economic evaluation – nivolumab vs docetaxel^a

	Nivolumab	Docetaxel	Increment
Economic evaluation within trial duration^b			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	1.184	1.030	0.154
QALYs	0.895	0.717	0.178
Incremental cost/LY gained			\$ [REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
Modelled economic evaluation (extrapolation to 7.5 years)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	1.786	1.220	0.565
QALYs	1.346	0.846	0.500
Incremental cost/LY gained			\$ [REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]

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

^a Results of economic evaluation were revised by taking into account the EFC fees.

^b No extrapolation but quality of life data and the cost of disease management (both pre- and post-progression) have been included.

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

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

- 6.50 For both comparisons, the extrapolation of trial survival data had the most effect on the results of economic evaluation. Both incremental life years (LYs) and quality-adjusted life years (QALYs) increased about 3 fold, from the trial observation to the modelled estimates; whereas the incremental costs increased to a lesser extent. The incremental cost-effectiveness ratio (ICER) for nivolumab versus pemetrexed or docetaxel was halved when trial results were extrapolated to 7.5 years.
- 6.51 The Pre-PBAC Response explored the effect of an RSA in which the calculation of the annual expenditure caps limits the cost of nivolumab per patient to that resulting from [REDACTED] administrations, resulting in an ICER of \$15,000/QALY - \$45,000/QALY vs. pemetrexed and \$45,000/QALY - \$75,000/QALY vs. docetaxel.

Table 10: Results of key sensitivity analyses

Label: model parameter	Assumption	Niv vs Pem		Niv vs Doc	
		\$/LY	\$/QALY	\$/LY	\$/QALY
Base case	–	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
SA.1: Point of extrapolation	Median duration of follow-up	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	End of available data	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
SA.2: Method of extrapolation	Weibull for both PFS and OS in both arms ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	Log-logistic for both PFS and OS in both arms ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
SA.3: Treatment effect of Pem before the extrapolation point ^b	Applying HR point estimates for OS and PFS (Pem vs Doc) as reported in Scagliotti 2009 ^c to the Doc survival curves ^a	\$ [REDACTED]	\$ [REDACTED]	–	–
	Applying lower CLs ^c of HRs for both	Dominated	Dominated	–	–

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Label: model parameter	Assumption	Niv vs Pem		Niv vs Doc	
		\$/LY	\$/QALY	\$/LY	\$/QALY
	PFS and OS ^a				
	Applying upper CLs ^c of HRs for both PFS and OS ^a	\$4 █████	\$ █████	-	-
SA.4: Treatment effect of Pem after the extrapolation point ^d	Applying a HR of 1.00 for both OS and PFS (Pem vs Doc) to the Doc survival curves ^a	\$ █████	\$ █████	-	-
SA.5: Time horizon	5 years	\$ █████	\$ █████	\$ █████	█████
	3 years ^a	\$ █████	\$ █████	\$ █████	\$ █████
SA.6: Nivolumab treatment duration	█████ infusions ^{a, e}	\$ █████	\$ █████	\$ █████	\$ █████
SA.7: Pre-progression disease management costs	Nivolumab pre-progression costs 20% less than the comparator arm	\$ █████	\$ █████	\$ █████	\$ █████
	Equal pre-progression costs in the two treatment arms	\$ █████	\$ █████	\$ █████	\$ █████
SA.3+SA.4	Applying HR point estimates for OS and PFS (Pem vs Doc) as reported in Scagliotti 2009 ^c to the Doc survival curves before the extrapolation point + applying a HR of 1.00 after this point ^a	\$ █████	\$ █████	-	-
	Applying lower CLs ^c of HRs for both OS and PFS (Pem vs Doc) to the Doc survival curves before the extrapolation point + applying a HR of 1.00 after this point ^a	\$ █████	\$ █████	-	-
	Applying upper CLs ^c of HRs for both OS and PFS (Pem vs Doc) to the Doc survival curves before the extrapolation point + applying a HR of 1.00 after this point ^a	\$ █████	\$ █████	-	-
SA.2+SA.3+SA.5 ^{b, f}	Extrapolation using Weibull model for PFS and OS in both arms + applying HR point estimates for OS and PFS (Pem vs Doc) as reported in Scagliotti 2009 ^c to the Doc survival curves before the extrapolation point + time horizon of 5 years ^a	█████	█████	\$ █████	\$ █████
SA.2+SA.3+SA.4+SA.5 ^f	Extrapolation using Weibull model for PFS and OS in both arms + applying HR point estimates for OS and PFS (Pem vs Doc) as reported in Scagliotti 2009 ^c to the Doc survival curves before the extrapolation point + applying a HR of 1.00 after this point + time horizon of 5 years ^a	\$ █████	\$ █████	\$ █████	\$ █████
Reanalyses using a cost of nivolumab per patient of \$ █████*					
Base case	-	\$ █████	\$ █████	\$ █████	\$ █████
SA.2: Method of extrapolation	Weibull for both PFS and OS in both arms ^a	\$ █████	\$ █████	\$ █████	\$ █████
	Log-logistic for both PFS and OS in both arms ^a	\$ █████	\$ █████	\$ █████	\$ █████
SA.5: Time horizon	5 years	\$ █████	\$ █████	\$ █████	\$ █████

Label: model parameter	Assumption	Niv vs Pem		Niv vs Doc	
		\$/LY	\$/QALY	\$/LY	\$/QALY
	3 years ^a	\$	\$	\$	\$

CL = confidence limit; Doc = docetaxel; HR = hazard ratio; LY = life year; Niv = nivolumab; OS = overall survival; Pem = pemetrexed; PFS = progression-free survival; QALY = quality-adjusted life year

^a Additional sensitivity analyses performed during the evaluation (or following the Pre-PBAC Response)

^b In SA.3, the re-submission's assumption that HR of 0.78 for OS and HR of 0.82 for PFS would be applied to the docetaxel survival estimates after the extrapolation point remained unchanged.

^c Scagliotti (2009) reported that the HRs for OS and PFS between pemetrexed and docetaxel were 0.78 [0.61, 1.00] and 0.82 [0.66, 1.02], respectively.

^d In SA.4, the re-submission's assumption of a HR of 1.00 for both OS and PFS between pemetrexed and docetaxel before the extrapolation point remained unchanged.

^e Arbitrary assumption: one infusion more than the base case ()

^f Change in the HRs for pemetrexed versus docetaxel was irrelevant to the economic analysis comparing nivolumab with docetaxel. SA.2+SA.3+SA.5(+SA.4) equalled to SA.2+SA.5 for this comparison.

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

Source: Table compiled during the evaluation. The base case analysis and the sensitivity analyses were conducted after correcting a few miscalculations in the re-submission and incorporating the updated EFC fees.

- 6.52 Results of the sensitivity analyses indicated that the model was sensitive to the point of extrapolation, the method of extrapolation and the assumed survival benefits associated with pemetrexed to be applied in the economic model particularly before the extrapolation point (for comparison of nivolumab vs pemetrexed only).
- 6.53 When the median durations of follow-up were used as the extrapolation points, the ICERs for nivolumab versus pemetrexed and nivolumab versus docetaxel increased from base case estimates of \$45,000/QALY - \$75,000/QALY to \$75,000/QALY - \$105,000/QALY and from \$75,000/QALY - \$105,000/QALY to \$105,000/QALY - \$200,000/QALY, respectively. This was due to: 1) the shape of OS and PFS Kaplan-Meier curves from CA209-057. After the two arms' survival curves crossed at about 6-7 months, the two curves continued to separate until about 20-21 months. Thus, truncation at around 20-21 months for OS and PFS, as in the base case, has resulted in an ICER most favourable to nivolumab; 2) the re-submission's assumption that HRs (pemetrexed vs docetaxel) would be applied to the docetaxel survival estimates after the truncation point. Assuming an earlier time point of extrapolation in the sensitivity analysis (e.g. using median duration of follow-up) meant more favourable survival estimates for pemetrexed applied earlier to the economic model, and, thus, has resulted in an ICER less favourable to nivolumab.
- 6.54 Extrapolating the OS and PFS with a Weibull model, i.e. the better fitting distribution to survival data on the basis of graphical inspection increased the ICERs from the base case \$45,000/QALY - \$75,000/QALY to \$75,000/QALY - \$105,000/QALY for nivolumab versus pemetrexed and from \$75,000/QALY - \$105,000/QALY to \$105,000/QALY - \$200,000/QALY for nivolumab versus docetaxel.
- 6.55 As noted earlier, the re-submission's assumption of applying favourable HRs for pemetrexed over docetaxel after the point of extrapolation, but not before this time point, was not reasonable. Sensitivity analyses showed that the ICER for nivolumab versus pemetrexed would increase by about 30% (\$45,000/QALY - \$75,000/QALY to \$75,000/QALY - \$105,000/QALY) if HR point estimates reported in Scagliotti (2009) (0.78 for OS and 0.82 for PFS) were applied to the economic model both before and after the extrapolation point.

- 6.56 The time horizon of the economic model was longer than the PBAC recommendation (7.5-year vs 5-year time horizon). Sensitivity analyses showed that the ICER result for nivolumab versus pemetrexed would change substantially if the time horizon varied between 1.5 years (before the median time to censoring for PFS) and 4 years. Later on, this economic model was less sensitive to the change in time horizon: the ICER increased by 6% (\$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$75,000/QALY) if a time horizon of 5 years was used. The time horizon had a relatively large impact on the result when comparing nivolumab with docetaxel.
- 6.57 During the evaluation, a number of multivariate sensitivity analyses were conducted. OS and PFS HRs between pemetrexed and docetaxel, and consequently the relative treatment effect of nivolumab versus pemetrexed, constituted an area of clinical and economic uncertainty given the exchangeability issues between CA209-057 and Scagliotti (2009) for the indirect comparison. The ICER for nivolumab versus pemetrexed was very sensitive to the change in HRs for pemetrexed versus docetaxel under the assumption that these HR estimates would be applied to the docetaxel survival data before the extrapolation time point, but assuming a HR of 1.00 for both PFS and OS between pemetrexed and docetaxel after the extrapolation point (\$45,000/QALY - \$75,000/QALY when upper confidence limits were used vs \$105,000 - \$200,000 QALY when the lower confidence limits were used).
- 6.58 When assuming a 5-year time horizon and extrapolating PFS and OS using a Weibull model for both arms:
- Nivolumab was associated with a minimal benefit of 0.013 QALY at a cost of \$██████, given an ICER of more than \$200,000/QALY, when compared with pemetrexed, if HRs for OS and PFS as reported in Scagliotti (2009) were applied to the docetaxel survival estimates before the extrapolation point but assuming a HR of 1.00 for both OS and PFS after this time point;
 - Nivolumab would be dominated by pemetrexed if HRs for OS and PFS as reported in Scagliotti (2009) were applied to the docetaxel survival estimates both before and after the point of extrapolation.

Drug cost/patient/course: \$██████.

- 6.59 The total drug cost per patient was \$██████. This was calculated using the proposed effective dispensed price, assuming an average patient body weight of 73.3 kg, requiring 219.9 mg of nivolumab. The dose was assumed to be supplied from 2 x 100 mg vials and 1 x 40 mg vial of nivolumab (allowing for wastage), with an average of ██████ infusions per patient, as observed from CA209-057 (without any extrapolation beyond trial observation). It was also assumed that 15% of the drug would be dispensed in public hospitals and 85% in private hospitals.
- 6.60 This was compared with a total cost of approximately \$██████ for pemetrexed therapy, based on a 10% sample of PBS data, and \$██████ for treatment with docetaxel, based on its usage in CA209-057.

Estimated PBS usage & financial implications

- 6.61 This re-submission was not considered by DUSC.

- 6.62 As for the original submission, the re-submission used an incidence-based approach to estimate the eligible population. This was appropriate.
- 6.63 The main differences between the re-submission and the original submission were:
- The proportion of patients diagnosed with NSCLC who were assumed to have non-squamous histology was reduced from 81.7% to 74.2%, as recommended by DUSC;
 - The proposed effective price for nivolumab was reduced;
 - The mean number of nivolumab infusions per patient was increased from [REDACTED] infusions to [REDACTED] infusions, in line with updated data from trial CA209-057; and
 - Drug wastage was included.
- 6.64 The re-submission's estimates for the proportion of patients receiving each treatment option were the same as those in the original submission. The assumptions in the treatment algorithms were based on clinical expert opinion, but there was no detail provided on how the information was elicited or the level of consensus among participants. These assumptions were a major source of uncertainty in the financial estimates and may have underestimated the uptake of nivolumab.
- 6.65 The estimated average cost of nivolumab per patient was uncertain, given:
- The duration of nivolumab treatment in practice may be longer than the estimate based on the 2-year minimum follow-up data from CA209-057, as 9.4% of patients in the trial were still receiving nivolumab;
 - The allowance for wastage of nivolumab may have been excessive.
- 6.66 The PBAC previously noted the DUSC's concerns about the potential for use of nivolumab beyond the restriction (paragraph 7.12, 5.07 nivolumab PSD, March 2016 PBAC Meeting). These concerns included the potential for use in earlier lines of therapy, use in patients with a performance status that is worse than those participating in the key trial (i.e. ECOG>1), and use beyond disease progression. The proposed restriction was amended in the re-submission to limit eligibility to patients with a performance score of 0 or 1.

Table 11: Estimated use and financial implications

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

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost PBS/MBS	\$	\$	\$	\$	\$
Net cost PBS/MBS March 2016	\$	\$	\$	\$	\$

^a Assuming [redacted] administrations per patient

^b Assuming [redacted] administrations per patient

^c Assuming, on average, one patient needs 219.9 mg of nivolumab with a body weight of 73.31 kg. To supply 219.9 mg of nivolumab, the re-submission assumed that 2 × 100 mg/10 mL vials and 1 × 40 mg/4 mL vials were required.

^d Assuming, on average, one patient needs 216.6 mg of nivolumab with a body weight of 72.2 kg. To supply 216.6 mg of nivolumab, the submission assumed 2 × 100 mg/10 mL vials and 0.42 × 40 mg/4 mL vials were required.

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

Source: Compiled during the evaluation

The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 and estimated net cost to the PBS would be \$60 - \$100 million.

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

- The uptake of nivolumab is likely be higher than assumed in the re-submission;
- The duration of nivolumab treatment in practice may be longer than the estimate based on trial CA209-057; and
- There is potential for use of nivolumab beyond the restriction.

These factors may be offset to some extent by the potentially excessive allowance for wastage of nivolumab.

Financial Management – Risk Sharing Arrangements

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

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

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

7 PBAC Outcome

7.1 The PBAC deferred its decision on the listing of nivolumab for the treatment of non-squamous NSCLC as there were concerns regarding the variation in the extent of effectiveness in patients over 75 years, especially given the high ICERs presented in the resubmission and doubts about the ability of the proposed RSA to achieve the sponsor's intended effect on these ICERs. The PBAC requested that the Department hold discussions with the sponsor in order to develop a proposal for a Managed Entry Scheme (MES) to address these concerns.

7.2 The PBAC reiterated its view that there is a clinical need for new treatments for

patients with non-squamous NSCLC. The PBAC noted, as previously, that the resubmission requested a second-line PBS listing for nivolumab, following progression on or after platinum-based chemotherapy.

- 7.3 The PBAC noted that the revised restriction provided in the resubmission and further clarification in the PSCR appropriately addressed the Committee's previous concerns with regard to performance status and the requirement for stable or responding disease in the continuing restriction. The PBAC also considered it appropriate to include the initiation criterion excluding patients who have received prior therapy with a PD-1 inhibitor.
- 7.4 The PBAC considered that the revised main comparator in the resubmission, pemetrexed, was appropriate. The resubmission also presented docetaxel, as in the original submission, as an alternate main comparator.
- 7.5 The PBAC considered the validity of the indirect comparison against pemetrexed to be highly uncertain, as there were transitivity issues across the trials, the HR from trial CA209-057 was not a reliable measure of the relative treatment effect of nivolumab versus docetaxel due to violation of the proportional hazards assumption, and the reliance on a retrospective analysis of the non-squamous NSCLC subgroup from Hanna (2004).
- 7.6 The PBAC considered that a claim of superior comparative effectiveness over pemetrexed was not well supported by the indirect comparison presented in the resubmission. However, the PBAC considered it likely that nivolumab provides an incremental clinical benefit compared with pemetrexed, also noting that the Committee had previously accepted the claim of superior comparative effectiveness over docetaxel (although this claim was strongest in patients who are PD-L1 positive).
- 7.7 The PBAC was concerned about the variation in the extent of effectiveness of nivolumab in patients over 75 years of age, with the prespecified subgroup analyses of CA209-057 suggesting that nivolumab may not have an incremental benefit over docetaxel in patients aged over 75 years (unstratified HR 0.90, 95% CI: 0.43, 1.87), and noting the abstract of an analysis (Landre et al, J Clin Oncol 34, 2016 (suppl; abstr 3070)⁵) which indicated that the survival benefit of nivolumab in patients older than 75 years appears uncertain. The PBAC considered that it was plausible that nivolumab, and other immunotherapies relying on stimulating an immune response, may prove to be less effective in older patients whose immune systems may no longer be able to respond to such a stimulus. The PBAC considered this likely reduced effectiveness in patients over 75 years of age to be a significant issue given that a large proportion of patients in Australian clinical practice would belong to this age group, with over 50% of patients over the age of 70 at diagnosis (and also noting the National Institute for Health and Care Excellence (NICE) appraisal of nivolumab for squamous NSCLC, which quoted the median age at diagnosis of 74 years in England and Wales⁶).
- 7.8 The PBAC recalled its previous consideration of the evidence for treatment effect

⁵ <http://meetinglibrary.asco.org/content/169457-176>

⁶ <https://www.nice.org.uk/guidance/GID-TAG506/documents/committee-papers>

variation by PD-L1 expression status in trial CA209-057. At that time, the PBAC had concluded that there was a qualitative difference in clinical benefit which constituted a signal suggesting important treatment effect variation according to PD-L1 expression testing as conducted in the trial. The PBAC noted that a range of predictive biomarkers were currently under development and encouraged the sponsor to submit data on these biomarkers should they subsequently prove useful for determining patient selection for treatment with immunotherapy.

- 7.9 The PBAC noted that there was insufficient data to form a full comparison of the safety profiles of nivolumab and pemetrexed, however recalled that it had previously accepted a claim of superior comparative safety over docetaxel.
- 7.10 Given the concerns regarding the validity of the indirect comparison of nivolumab vs. pemetrexed, the PBAC considered that the base case ICER against pemetrexed (\$45,000/QALY - \$75,000/QALY) could not be relied upon. The PBAC considered that the incremental cost per QALY gained for nivolumab over docetaxel presented in the resubmission's base case (\$75,000/QALY - \$105,000/QALY) was very high, and noted that although the resubmission had modified aspects of the model inputs, there was residual disagreement about a number of assumptions favourable to nivolumab as raised by the ESC, in particular the method of extrapolation and time horizon. The PBAC considered that these optimistic assumptions in the economic model were likely to produce an underestimate of the true ICER. However, in the context of high clinical need, the PBAC advised that the reduced, although still high ICER (\$75,000/QALY - \$105,000/QALY vs. docetaxel) proposed in the Pre-PBAC Response with a risk share arrangement (RSA) would be in an acceptable range should the Committee's concerns regarding the likely variation in the effectiveness of nivolumab with regards to age be adequately mitigated through a MES proposal developed between the Department and the sponsor (see further detail below). The PBAC foreshadowed that, if an adequate MES could be developed, this would provide earlier access to eligible patients for whom there is a high clinical need whilst the Committee's concerns about variation in the effectiveness of nivolumab are addressed.
- 7.11 The PBAC also advised that a prerequisite for any recommendation for PBS listing involving the RSA proposal as presented in the Pre-PBAC Response would be sufficient reassurance that this would actually achieve the ICER of \$15,000/QALY - \$45,000/QALY vs. pemetrexed (or \$75,000/QALY - \$105,000/QALY vs. docetaxel) as claimed. The PBAC noted that, in addition to the cost per patient, each annual expenditure cap in an RSA also relies on less certain estimates such as numbers of eligible patients and uptake rates. In addition, there would be lags in achieving the estimated number of patients for each year, and in these eligible patients reaching the proposed limit of ■ administrations, both of which would affect how the RSA would relate to the cost per patient for nivolumab contributing to the ICER. The PBAC therefore requested that these matters also be discussed between the Department and the sponsor, and addressed for PBAC reconsideration alongside the fuller MES proposal as outlined below.
- 7.12 The PBAC considered that the financial implications presented in the resubmission may be underestimated due to potential leakage beyond the restriction and uncertainty around treatment duration, however considered that an RSA providing an overall cap based on patient numbers as well as the numbers of doses per patient

would offer some certainty of the overall costs to the PBS.

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

- 7.18 The PBAC noted that the fuller MES proposal would need to show how the number of patients aged 75 years or over subsidised via the PBS would be recorded, together with the number of prescriptions dispensed to these patients in order to indisputably calculate the amount of any rebate that might be required at the completion of this component of the MES. If a significantly reduced effectiveness is demonstrated compared to the appropriate comparators, consideration will then also need to be given as to whether the restriction is tightened with reference to age, or the restriction remain unchanged and the rebating system introduced, or some other transitional arrangement.

Outcome:

Deferred

8 Context for Decision

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

9 Sponsor's Comment

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