

4.02 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 minor re-submission sought PBS listing of nivolumab for non-squamous cell non-small cell lung cancer (NSCLC) and squamous cell NSCLC by addressing the issues raised by the PBAC in its November 2016 deferral of nivolumab for NSCLC.
- 1.2 To support the listing, the minor re-submission presented:
 - analyses assessing potential treatment effect modification of nivolumab based on PD-L1 expression status;
 - a proposal for a MES relating to PD-L1 expression;
 - analyses assessing potential treatment effect modification of nivolumab based on age (in those aged 75 years or more);
 - a proposal for a managed entry scheme (MES) for nivolumab for patients aged 75 years or more;
 - an age-based risk sharing arrangement (RSA) as an alternative to the MES for age; and
 - a revised overall RSA.

2 Requested listing

- 2.1 As the minor re-submission did not present an amended requested listing, the listing and the requested dispensed price was assumed to be the same as that requested at the November 2016 PBAC meeting, including any amendments recommended by the PBAC at that meeting.

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

3 Background

- 3.1 The PBAC considered nivolumab for the treatment of squamous NSCLC and non-squamous NSCLC at the March and November 2016 PBAC meetings. At the November 2016 PBAC meeting, the PBAC deferred its decision pending proposals for an MES relating to patients aged 75 years or older years and biomarker status, as well as for an RSA. A summary of the November 2016 PBAC's considerations in relation to the MES and RSA for nivolumab, and the information provided in response by the sponsor, are presented in the table below.

November 2016 PBAC meeting consideration	March 2017 minor re-submission (current)
<p>The PBAC [also] maintained that there was no clear predictive effect of PD-L1 expression on the comparative effectiveness of nivolumab in trial CA209-017 (paragraph 7.7, 7.06 nivolumab PSD, November 2016) and 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 [CA209-057] (paragraph 7.8, 7.07 nivolumab PSD, November 2016).</p> <p>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 (paragraph 7.7, 7.06 nivolumab PSD and paragraph 7.8, 7.07 nivolumab PSD, November 2016).</p> <p>The PBAC requested a proposal for a MES for nivolumab for both squamous and non-squamous cell NSCLC address this concern.</p>	<ul style="list-style-type: none"> • Sub-group analyses to examine the treatment effect of PD-L1 status in a range of meta-analyses for nivolumab in NSCLC, melanoma, cancer, and all PD pathway drugs in melanoma or cancer. The minor re-submission contended that patients in general derive benefit from nivolumab irrespective of PD-L1 status. Paragraphs 6.{7} to 6.{19} refer. • An MES was proposed. Paragraphs 6.{20} to 6.{25} refer.
<p>The PBAC queried the effectiveness of nivolumab in patients aged 75 years or older, in both squamous and non-squamous cell NSCLC (paragraphs 7.1, 7.06 and 7.07 nivolumab PSD, November 2016 meeting).</p> <p>The PBAC requested a proposal for a MES for nivolumab for both squamous and non-squamous cell NSCLC to address this concern.</p>	<ul style="list-style-type: none"> • Sub-group analyses to examine the treatment effect of age in a range of meta-analyses for nivolumab in NSCLS, melanoma and cancer, and PD pathway treatments in NSCLS, melanoma, and cancer. The minor re-submission contended that there is sufficient data to show that age is not a treatment effect modifier. Paragraphs 6.{26} to 6.{48} refer. • An MES was proposed. The minor re-submission contended that an MES is not practical or informative, and in the event that PBAC does not accept its contention that age is not a treatment modifier, proposed a modified RSA to address any remaining uncertainty. Paragraphs 6.{49} to 6.{56} refer.
<p>The PBAC requested the Department and the sponsor to also discuss a RSA, and noted that this should be derived using a cost per patient multiplied by the number of eligible patients, and that potential patient uptake and dosage lags be factored into the proposed expenditure caps (paragraph 7.9, 7.06 nivolumab PSD and paragraph 7.11, 7.07 nivolumab PSD, November 2016).</p>	<p>The minor re-submission presented an RSA which outlines the patient number and total patient cost. Paragraphs 6.{59} to 6.{66} refer.</p>

- 3.2 In requesting proposals for MESs for age and PD-L1 status, the PBAC advised that the MES structure should be based on a meta-analysis across comparative trials of nivolumab in NSCLC. Consideration should also be given to:
- a meta-analysis based on individual patient data;
 - an expanded meta-analysis including comparative trials of other existing and emerging immunotherapies with the same or similar mechanism of action on the programmed cell death pathway, and;
 - a further expansion to include comparative trials across other cancer types (paragraph 7.13, 7.06 nivolumab PSD and paragraph 7.15, 7.07 nivolumab PSD, November 2016).
- 3.3 The PBAC noted that the sponsor provided squamous and non-squamous NSCLC patients with nivolumab through a Named Patient Program (BMSA NPP) and a Patient Access Program. The BMSA NPP commenced in March 2015 (for squamous NSCLC patients) and June 2015 (for non-squamous NSCLC patients) and enrolled patients up until TGA registration in March 2016. A total of [REDACTED] non-squamous and [REDACTED] squamous NSCLC patients were enrolled in the BMSA NPP. The Patient Access Program commenced in March 2016 after TGA registration with a total of [REDACTED] patients having been treated since commencement. It is unclear which of the two programs are being used as the data source within the submission.

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

4 Clinical place for the proposed therapy

- 4.1 Unchanged from previous submission.

5 Comparator

- 5.1 Unchanged from previous submission.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The minor re-submission referenced a number of trials already considered by the PBAC. New clinical trials were also presented in the minor re-submission, in-line with the PBAC’s suggestion that an expanded meta-analysis including comparative trials of other existing and emerging immunotherapies with the same or similar mechanism

of action on the programmed cell death pathway, and a further expansion to include comparative trials across other cancer types could be included. Table 1 summarises the trials presented in the minor re-submission.

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

Trial ID	Protocol title/ Publication title	Publication citation	Previously considered*
Direct randomised trials – nivolumab for second-line treatment of NSCLC			
CA209-017 (017)	Clinical Study Report for Study CA209-017 Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer.	Brahmer J, Reckamp K, Crino L et al. N Engl J Med 2015;373:123-35.	Nivolumab (March & November 2016)
CA209-057 (057)	Clinical Study Report for Study CA209-057 Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer.	Borghaei H, Paz-Ares, L. Horn L, et al. N Engl J Med 2015; 373:1627-39	
Single-arm study data – nivolumab for second-line treatment of NSCLC			
CHECKMATE-153	Is Nivolumab Safe and Effective in Elderly and ECOG PS 2 Patients With NSCLC? Results of CheckMate 153.	Spigel D, Schwartzberg L, Waterhouse D. et al. Poster presented at the International Association for the Study of Lung Cancer 17th World Conference on Lung Cancer; December 4–7, 2016; Vienna, Austria	No
Italian Expanded Access Program	Efficacy and Safety of Nivolumab in Elderly Patients With Advanced Squamous NSCLC Participating in the Expanded Access Program in Italy.	Grossi F, Crinò L, Misino A. et al. Poster presented at the European Society for Medical Oncology 41st Congress; October 7–11, 2016; Copenhagen, Denmark.	No
Direct randomised trials – PD pathway treatments for NSCLC			
Keynote-010 (KN-010)	Pembrolizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial.	Herbst R, Baas P, Kim D-W et al. Lancet 2016; 387: 1540–50	No
Keynote-024 (KN-024)	Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer (KEYNOTE-024).	Reck M, Rodríguez-Abreu D, Robinson A. N Engl J Med 2016;375:1823-33.	No

Trial ID	Protocol title/ Publication title	Publication citation	Previously considered*
OAK	Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial.	Rittmeyer A, Barlesi F, Waterkamp D et al. Lancet 2016. http://dx.doi.org/10.1016/S0140-6736(16)32517-X	No
Direct randomised trials – nivolumab for treatment of other cancer types			
CA209-037 (037)	Clinical Study Report for Study CA209-037 Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial	Weber J, D'Angelo S, Minor D, Hodi F et al. Lancet Oncol. 2015;16(4):375-84.	No
CA209-066 (066)	Clinical Study Report for Study CA209-066 Nivolumab in previously untreated melanoma without BRAF mutation	Robert C, Long GV, Brady B, et al. N Engl J Med 2015; 372(4):311-9.	Nivolumab (July 2015)
CA209-025 (025)	Clinical Study Report for Study CA209-025 Nivolumab versus everolimus in advanced renal-cell carcinoma	Motzer RJ, Escudier B, McDermott DF, et al. N Engl J Med 2015; 373 (191):1803-13.	Nivolumab (July 2016)
CA209-141 (141)	Clinical Study Report for Study CA209-141		No
Direct randomised trials – PD pathway treatments for other cancer types			
Keynote-006 (KN-006)	Pembrolizumab versus ipilimumab in advanced melanoma.	Robert C, Schachter J, Long G et al. N Engl J Med 2015;372:2521-32	Pembrolizumab (March 2016) & Nivolumab (November 2015)

* Previously considered by the PBAC
Source: the minor re-submission

- 6.4 The literature search conducted for the minor re-submission appeared to be reasonable (an independent search did not identify any further potentially relevant trials/studies), however it was not clear that all relevant trials/studies were included as inclusion of trials was restricted to phase III monotherapy trials that presented overall survival (OS), where data was available to the sponsor.
- 6.5 The key features of the comparative and non-comparative studies of nivolumab and other existing and emerging immunotherapies with the same or similar mechanism of action on the programmed cell death pathway, in addition to the outcomes reported and presented in the minor re-submission, are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes reported
Direct randomised trials – nivolumab for second-line treatment of NSCLC					
CA209-017 (017)	272	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 ^a	Patients with <u>squamous cell NSCLC</u> (unselected for PD-L1 status) who had failed platinum-based chemotherapy	Overall survival (HR [95% CI]) in the following pre-defined sub-groups: a) <65 and ≥65 years b) <75 and ≥75 years c) <65, 65-<75 and ≥75 years d) PD-L1 expression cut-off of 1% (ie, <1% and ≥1%)
CA209-057 (057)	582	R, OL Database lock March 2015 (follow-up 13.2 months) and database lock July 2015 (most updated: follow-up 17.1 months)	Low for OS High for AEs and QoL ^b	Patients with <u>non-squamous cell NSCLC</u> (unselected for PD-L1 status) who had failed platinum-based chemotherapy	Overall survival (HR [95% CI]) in the following pre-defined sub-groups: a) <65 years b) ≥65-<75 years c) ≥75 years d) ≥65 years e) PD-L1 expression cut-off of 1%
Single-arm study data – nivolumab for second-line treatment of NSCLC					
CHECKMATE-153	1375	R, OL Follow-up of 6.9 months	Low for OS	Patients with advanced metastatic NSCLC (<u>squamous or non-squamous</u>) treated with ≥1 prior systemic therapy	Median, 6-month overall survival and 1-year overall survival (95% CI) in the following sub-groups: a) <70 years b) ≥70 years c) ECOG PS0-1 d) ECOG PS2. Additional analysis for the PBAC of median overall survival in patients aged ≥75 years of age with ECOG PS of 0, 1 and 2
Italian Expanded Access Program	371	NR, OL Median follow-up of 7 months	Low for OS, High for response to Tx	Patients with stage IIIB/IV <u>squamous</u> NSCLC with disease relapse after receiving ≥1 prior treatment	Response to treatment and overall survival in all patients and in patients aged ≥75 years
BMS Australia named patient program (BMSA NPP)	1554	OL Median follow-up NR		Patients with squamous or non-squamous NSCLC, treatment provided at no cost to patients or institutions	a) Proportion aged ≥75 years with an ECOG of 0-1 b) Average duration of Tx
Direct randomised trials – PD pathway treatments for NSCLC					
Keynote-010 (KN-010)	1034	R, OL Median follow-up of 13.1 months	Low for OS	Patients previously treated NSCLC and PD-L1 expression >1%	Overall survival (HR [95% CI]) for patients: a) <65 years b) ≥65 years c) PD-L1 expression cut-off of 50%

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Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes reported
Keynote-024 (KN-024)	305	R, OL Median follow-up of 11.2 months	Low for OS	Patients with previously untreated advanced NSCLC and PD-L1 expression \geq 50%	Disease progression or death (HR [95% CI]) for patients: a) <65 years b) \geq 65 years c) PD-L1 expression cut-off of 50%
OAK	850	R, OL Median follow-up of 21 months	Low for OS	Patients with previously treated <u>squamous</u> or <u>non-squamous</u> NSCLC	Overall survival (HR [95%CI]) in the following pre-defined sub-groups: a) <65 years b) \geq 65 years
Direct randomised trials – nivolumab for treatment of other cancer types					
CA209-037 (037)	390	R, OL Median follow-up of 15.34 months for nivolumab and 13.67 months for the investigator's choice chemotherapy group	Low for OS	Patients with advanced (unresectable or metastatic) melanoma	Overall survival (HR [95% CI]) in the following pre-defined sub-groups: a) <65 years b) \geq 65 years c) \geq 65-<75 years d) \geq 75 years e) PD-L1 expression cut-off of 1%
CA209-066 (066)	583	R, DB Follow-up duration not reported	Low for OS	Patients with previously untreated, unresectable or metastatic melanoma	Overall survival (HR [95% CI]) in the following pre-defined sub-groups: a) <65 years b) \geq 65-<75 years c) \geq 75 years d) PD-L1 expression cut-off of 1%
CA209-025 (025)	1054	R, OL Median follow-up 18.25 months for nivolumab and 17.22 months for everolimus	Low for OS	Patients with advanced or metastatic clear-cell renal cell carcinoma who have received prior anti-angiogenic therapy	Overall survival (HR [95% CI]) in the following pre-defined sub-groups: a) <65 years b) \geq 65 years c) \geq 65-<75 years d) \geq 75 years e) PD-L1 expression cut-off of 1%
CA209-141 (141)	361	R, OL Median follow-up 5.3 months for nivolumab and 4.5 months for investigators choice chemotherapy group	Low for OS	Patients with recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck	Overall survival (HR [95% CI]) in the following sub-groups: a) <65 years b) \geq 65-<75 years c) \geq 75 years d) PD-L1 expression cut-off of 1%
Direct randomised trials – PD pathway treatments for other cancer types					

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes reported
Keynote-006 (KN-006)	834*	R, Controlled Median follow-up 7.9 months	Low for OS	Patients with advanced melanoma	Overall survival (HR [95% CI]) in the following pre-defined sub-groups: a) <65 years b) ≥75 years c) PD-L1 expression cut-off of 1%

NR=not reported; OL=open-label, R=randomised, Tx=treatment

^a Table 2, Executive summary of 5.06 nivolumab (squamous) COM 03-2016.docx

^b Table 2, Executive summary of 5.07 nivolumab (non-squamous) COM 03-2016.docx

* Based on information reported in Robert et al 2015. Note: the PSD for nivolumab from the July 2016 PBAC meeting, reported 821 patients

Source: Compiled during the evaluation

PD-L1 expression

6.6 In-line with the suggestions made by the PBAC in its November 2016 consideration of the nivolumab major re-submissions regarding the treatment effect of nivolumab based on PD-L1 expression levels, the minor re-submission presented the following:

- A meta-analysis of the sub-groups of patients with PD-L1 expression <1% or ≥1% in the nivolumab NSCLC trials (CA209-017 and -057).
- A meta-analysis of the sub-groups of patients of patients with PD-L1 expression <1% or ≥1% in the nivolumab trials (any indication), with the addition of two trials in melanoma (CA209-037 and -066), one trial in renal cell carcinoma (CA209-025) and one trial in head and neck cancer (CA209-141) to those in NSCLC (CA209-017 and -057).
- A meta-analysis of the sub-groups of patients with PD-L1 expression <1% or ≥1% in the nivolumab trials (any indication; CA209-017 and -057, -037, -066, -025, -141) with the addition of other PD-pathway treatment trials (pembrolizumab [Keynote-006]).
- Further meta-analysis of the sub-groups of patients with PD-L1 expression <50% or ≥50% in two pembrolizumab trials (Keynote-010 and -024).

Efficacy data (PD-L1)

6.7 The PBAC has previously accepted that no clear predictive effect of PD-L1 status on the comparative effectiveness of nivolumab was demonstrated in the pivotal clinical Trial CA209-017 [squamous NSCLC], therefore it would be appropriate to allow treatment for patients regardless of PD-L1 status (paragraph 7.3, 5.06 nivolumab PSD, March 2016).

6.8 The PBAC previously considered the evidence for treatment effect variation by PD-L1 status in Trial CA209-057 [non-squamous NSCLC], noting that nivolumab was associated with a median OS more than twice than that observed for docetaxel in PD-L1 positive patients, however the median OS 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).

- 6.9 Based on the concerns expressed regarding the potential predictive value of PD-L1 status among those with non-squamous NSCLC in Trial CA209-057, the minor re-submission conducted an overall survival sensitivity analysis of all randomised subjects alive at 3 months for the sub-group of patients with no tumour PD-L1 expression (HR=████; 95% █████, █████; n=████) and provided a comparison to all randomised subjects with no PD-L1 expression (HR=████; 95% CI: █████, █████; n=████), indicating that PD-L1 negative patients alive 3 months post treatment initiation derive a clinically significant and clinically relevant OS benefit from nivolumab. Exploration of baseline characteristics among PD-L1 negative patients dying and those not dying less than 3 months post treatment initiation signalled an imbalance in ECOG performance-status between the groups, with a greater proportion of those experiencing early events having an ECOG performance-status of 1 (rather than 0).
- 6.10 Table 3 presents the overall survival (HR [95% CI]) reported for various pre-defined subgroups based on PD-L1 expression in the trials and subsequent meta-analyses, with accompanying tests for interaction.

Table 3: Overall survival (HR [95% CI]) reported in the pre-defined sub-groups by PD-L1 expression as reported in the trials

Trial	Indication	Comparison	N (%) ^a	HR (95% CI) for OS		Test for interaction [*]
				PD-L1 <1%	PD-L1 ≥1%	
017 ^b	Sq NSCLC (2L)	NIV v DOC	272 (38.9)	0.58 (0.37, 0.91)	0.70 (0.46, 1.08)	NS
057	Non-Sq NSCLC (2L)	NIV v DOC	582 (57.7)	0.90 (0.66, 1.24)	0.59 (0.43, 0.81)	0.0646 ^c
037	Melanoma (2L)	NIV v IC	405 (27.1)	0.52 (0.38, 0.71)	0.52 (0.38, 0.71)	0.012^d
066 ^b	Melanoma (1L)	NIV v DAC	418 (64.6)	0.63 (0.37, 1.07)	0.28 (0.17, 0.47)	<0.05
KN-006 ^e	Melanoma (1L and 2L)	PEM v IPI	811 (NR)	0.91 (0.49, 1.69)	0.55 (0.41, 0.84)	NS
				1.02 (0.56, 1.85)	0.58 (0.42, 0.79)	NS
025	AMCCRCC (2L)	NIV v EVE	821 (23.9)	0.52 (0.38, 0.71)	0.52 (0.38, 0.71)	NS
141	RMSCCHN (2L)	NIV v IC	361 (30.7)	0.89 (0.54, 1.45)	0.55 (0.36, 0.83)	0.46 ^f
Meta-analysis – nivolumab in NSCLC (017, 057)				0.74 (0.49, 1.14) I ² =59.3%	0.63 (0.49, 0.81) I ² =0%	NS
Meta-analysis – nivolumab in melanoma (037, 066)				0.98 (0.41, 2.32) I ² =81.3%	0.45 (0.19, 1.06) I ² =87.8%	NS
Meta-analysis – PD pathway in melanoma (037, 066, KN-006)				0.97 (0.67, 1.42) I ² =44.7%	0.52 (0.38, 0.71) I ² =64.5%	<0.05
Meta-analysis – nivolumab in cancer (017, 057, 037, 066, 025, 141)				0.83 (0.66, 1.03) I ² =45.9%	0.59 (0.46, 0.75) I ² =57.3%	<0.05
Meta-analysis – PD pathway in cancer (017, 057, 037, 066, KN-006, 025, 141)				0.84 (0.70, 1.01) I ² =28.8%	0.58 (0.49, 0.70) I ² =41.3%	<0.05
				PD-L1 <50%	PD-L1 ≥50%	
KN-010	PD-L1+ (≥1%) NSCLC (2L)	PEM v DOC	1033 (NR)	0.76 (0.60, 0.96)	0.53 (0.40, 0.70)	NS
KN-024	PD-L1+ (≥50%) NSCLC (1L)	PEM v IC	305 (0)	NA	0.60 (0.41, 0.89)	NE

AMCCRCC=advanced or metastatic clear-cell renal cell carcinoma; ATE=atezolizumab; CI=confidence interval; DAC=dacarbazine; DOC=docetaxel; EVE=everolimus; HR=hazard ratio; IC=investigator choice; IPI=ipilimumab; NA=not applicable; NE=not estimable; NIV=nivolumab; NR=not reported; NS=not statistically significant at the 5% level; NSCLC=non-small cell lung cancer; Non-Sq NSCLC=non-squamous non-small cell lung cancer; NR=not reported; PD-L1+=PD-L1 positive; PEM=pembrolizumab; RMSCCHN=recurrent or metastatic squamous cell carcinoma of the head and neck; Sq NSCLC=squamous non-small cell lung cancer; TFI=test for interaction; 1L=first-line; 2L=second-line.

Bold values indicate statistically significant differences

Additional meta-analyses conducted in StatsDirect and tests for interaction conducted during the evaluation (if not reported in the trial reports)

* approximated using a test for interaction relevant to relative risk estimates (<0.05 or NS), otherwise as reported in the CSR
^a N=total in trial and (%)=proportion with PD-L1 expression <1% or <50% (depending on the analysis) of patients with a PD-L1 assessment

^b could not independently verify during the evaluation

^c Table 7.5.2-1, p132 of the CA209-057 trial report. Statistically significant differences indicated at the 5% (TFI p=0.0004) and 10% (TFI p=0.0002) PD-L1 expression levels

^d Table 7.5.4-1, p128 of the CA209-037 trial report. Similar differences at 5% and 10% PD-L1 expression levels

^e Figure 2, p2526 of Robert et al 2015. Results reported for pembrolizumab 10 mg/kg q2w versus ipilimumab and pembrolizumab 10 mg/kg q3w versus ipilimumab (q2w reported first). Treated as two trials in the meta-analysis.

^f Table 7.7-2, p102 of the CA209-141 trial report

Source: pp39-45 of the minor re-submission

- 6.11 Table 4 presents the overall survival data assessed in four categories of PD-L1 expression reported in the OAK trial.

Table 4: Overall survival (HR [95% CI]) reported in the pre-defined sub-groups by PD-L1 expression as reported in the OAK trial

PD-L1 expression	HR (95% CI)
TC3 or IC3 (PD-L1 expression \geq 50% of tumour cells or \geq 10% of infiltrating immune cells)	0.41 (0.27, 0.64)
TC2/3 or IC2/3 (PD-L1 expression \geq 5% of tumour cells or infiltrating immune cells)	0.67 (0.49, 0.90)
TC1/2/3 or IC1/2/3 (PD-L1 expression \geq 1% of tumour cells or infiltrating immune cells)	0.74 (0.58, 0.93)
TC0 or IC0 (PD-L1 expression low or undetectable on tumour cells or infiltrating immune cells)	0.75 (0.59, 0.96)

TC=tumour cells, IC=infiltrating immune cells

Test for interaction comparing 'TC1/2/3 or IC1/2/3' and 'TC0 or IC0' was not significant

Source: Figure 13, p41 of the minor re-submission

- 6.12 The data from the individual trials indicated that a statistically significant improvement in overall survival was associated with treatment with nivolumab compared with its comparator in Trial CA09-017 (squamous NSCLC versus docetaxel) and Trial CA209-025 (renal cell carcinoma versus everolimus) among those with less than 1% of cells expressing PD-L1. The remaining five trials demonstrated a statistically significant improvement in overall survival among those with 1% or more cells expressing PD-L1.
- 6.13 There was significant heterogeneity observed for some of the meta-analyses indicating likely inappropriate combination of trial results and also acknowledging that the three PD pathway treatments considered use different biomarker tests and PD-L1 cut-off levels.
- 6.14 The meta-analyses conducted for those with less than 1% of cells expressing PD-L1 indicated no differences between nivolumab or PD pathway treatments and its comparators in terms of overall survival in the treatment of NSCLC, melanoma or "cancer".
- 6.15 Conversely, the meta-analyses conducted for those with 1% or more cells expressing PD-L1 indicated that a statistically significantly improved overall survival compared with the comparators was associated with nivolumab in the treatment of NSCLC and "cancer", but not melanoma and for PD pathway treatments in the treatment of NSCLC, melanoma and "cancer".
- 6.16 The test for interaction (comparing those with less than 1% and those with 1% or more cells expressing PD-L1) indicated that PD-L1 expression was a treatment effect modifier for nivolumab in the treatment of melanoma from data reported in Trials CA209-037 and -066 and in the meta-analyses of PD pathway treatments in melanoma, and meta-analyses of nivolumab and PD pathway treatments in the treatment of any cancer.
- 6.17 The sponsor claimed that cancer patients in general derive benefit from nivolumab versus current standards of care, irrespective of PD-L1 status. The sponsor asserted that practical and clinical issues associated with PD-L1 testing necessitate a more specific review of the data by indication/line of therapy before specific conclusions

can be made with respect to the predictive value of PD-L1. Although potentially reasonable based on the data presented, should nivolumab act through the PD-L1 pathway, it was unclear why indication or line of therapy would alter its effect. The PBAC considered this claim to be reasonable given that PD-L1 status can change depending on tumour stage and progression.

- 6.18 The PBAC considered that the meta-analyses of pre-defined subgroups in the nivolumab randomised trials based on PD-L1 expression presented in the submission did not indicate a clear predictive effect of PD-L1 status on the comparative effectiveness of nivolumab. Based on this evidence, the PBAC therefore considered that nivolumab should be available to a broad population of patients irrespective of PD-L1 status.

Proposed Managed Entry Scheme - (PD-L1)

- 6.19 The sponsor maintained that the data previously presented to the PBAC supports a broad PBS listing for nivolumab for the treatment of squamous and non-squamous NSCLC, irrespective of PD-L1 status. However, the sponsor proposed a MES approach for PD-L1.
- 6.20 The minor re-submission proposed the following for the MES:
- submission of a comprehensive scan on biomarker research in NSCLC annually for 5 years: specifically, a list of trials that are planned or initiated (with expected completion dates) that assess the influence of PD-L1 expression or other biomarkers on the efficacy of nivolumab in NSCLC, nivolumab across indications, and other immunotherapies in NSCLC and across indications;
 - provision of an updated meta-analysis or data review, should additional data on nivolumab in NSCLC become available, with a report expected in the first instance based on a final report of nivolumab in the first-line treatment of NSCLC from trial CA209-227 due in the [REDACTED]; and
 - provision of a co-dependent reimbursement submission should data from CA209-227 or future nivolumab clinical trial data across other indications demonstrate that PD-L1 or another biomarker is clinically relevant to determining patient selection for treatment with nivolumab.
- 6.21 The minor re-submission proposed that the cost associated with the comprehensive scan on biomarker research in NSCLC be shared with other sponsors should other therapies be listed on the PBS for NSCLC indications. The PBAC had no objections to this proposal.
- 6.22 The minor re-submission also provided a table of trials from clinical trials.gov specific to biomarker research. An independent search located no further relevant trials or studies. The majority (eight) of the 12 identified studies involve assessment of pembrolizumab, with three for nivolumab and one for durvalumab. The earliest completion dates for the studies is September 2017. Given many of the ongoing studies involve pembrolizumab, there is a possibility that the relevance of any biomarkers deemed relevant to pembrolizumab may not be apparent for nivolumab given different biomarker tests may be used, as well as differing cut-off values, as is the current case for PD-L1.

- 6.23 On review, the PBAC considered that, rather than a formal MES, the sponsor should commit to an ongoing review of randomised trial data to address residual uncertainty regarding possible biomarkers predicting treatment effect modification of nivolumab in NSCLC and/or other anti-PD1 therapy in NSCLC. The PBAC also requested that the sponsor indicate what potential there would be for retrospective analyses of samples from clinical trial participants to enable further investigations if new biomarkers were identified.
- 6.24 The PBAC considered that if a biomarker that modified the comparative treatment effect of nivolumab was identified in the future, then a submission to the committee would be required and would have the following potential outcomes:
- If a subgroup with a better outcome was identified – no increase to the price of nivolumab;
 - If a subgroup with no effect or a worse outcome was identified – the restriction should be narrowed to exclude these patients from PBS subsidised treatment, and the RSA would need to be adjusted accordingly.

Effectiveness of nivolumab in patients 75 years or older

- 6.25 In order to address the PBAC's concerns from the November 2016 meeting regarding the treatment effect of nivolumab in patients aged 75 years or more, the minor re-submission presented the following analyses:
- A meta-analysis of the sub-groups of patients in the nivolumab NSCLC trials (CA209-017 and -057) aged <65 years, ≥65 years, 65-74 years and ≥75 years;
 - Sub-group analyses of those aged ≥75 years in three single-arm observational studies of the use of nivolumab in the treatment of NSCLC (CHECKMATE-153 [squamous and non-squamous]; the Italian Expanded Access Program [squamous]; and the BMS Australian named patient program (BMSA NPP) [squamous and non-squamous]);
 - A meta-analysis of the sub-groups of patients aged <65 and ≥65 years in the nivolumab NSCLC trials (CA209-017 and -057) with the addition of other PD-pathway treatment trials (pembrolizumab [Keynote-010 and -024] and atezolizumab [OAK]) for NSCLC (as data only reported for those aged <65 and ≥65 years for non-nivolumab trials);
 - A meta-analysis of the sub-groups of patients aged ≥75 years in the nivolumab trials (any indication), with the addition of two trials in melanoma (CA209-037 and -066), one trial in renal cell carcinoma (CA209-025) and one trial in head and neck cancer (CA209-141) to those in NSCLC (CA209-017 and -057); and
 - A meta-analysis of the sub-groups of patients aged <65 and ≥65 years in the nivolumab trials (any indication; CA209-017 and -057, -037, -066, -025, -141) with the addition of other PD-pathway treatment trials (pembrolizumab [Keynote-010, -024, -006] and atezolizumab [OAK]) in any indication (as data only reported for those aged <65 and ≥65 years for non-nivolumab trials).

Efficacy data (patients aged 75 years or older)

6.26 The HR for median overall survival in each age subgroup within each trial and the meta-analyses are summarised in Table 5.

Table 5: Overall survival (HR [95% CI]) reported in the pre-defined sub-groups by age as reported in the trials

Trial	Indication	Comparison	N (%) ^a	HR (95% CI) for OS		Test for interaction*
				<75 years	≥75 years	
017 ^b	Sq NSCLC (2L)	NIV v DOC	272 (89.3)	0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	<0.05
057 ^c	Non-Sq NSCLC (2L)	NIV v DOC	582 (92.6)	NR	0.75 (0.55, 1.00)	NE
037 ^g	Melanoma (2L)	NIV v IC	1033 (94.6)	NR	0.75 (0.55, 1.00)	NE
066 ^h	Melanoma (1L)	NIV v DAC	850 (92.1)	NR	0.75 (0.55, 1.00)	NE
025 ^j	AMCCRCC (2L)	NIV v EVE	821 (91.0)	NR	0.75 (0.55, 1.00)	NE
141 ^k	RMSCCHN (2L)	NIV v IC	361 (95.0)	NR	NR	NE
Meta-analysis – nivolumab in NSCLC (017, 057); I ² =33.2%				0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	<0.05
Meta-analysis – nivolumab in melanoma (037, 066); I ² =62.5%				0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS
Meta-analysis – nivolumab in cancer (017, 057, 037, 066, 025); I ² =65.4%				0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS
				<65 years	≥65 years	
017 ^b	Sq NSCLC (2L)	NIV v DOC	272 (55.9)	0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS
057 ^c	Non-Sq NSCLC (2L)	NIV v DOC	582 (58.2)	0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS
KN-010 ^d	PD-L1+ (≥1%) NSCLC (2L)	PEM v DOC	1033 (58.5)	0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS
OAK ^f	NSCLC (2L)	ATE v DOC	850 (53.3)	0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS
037 ^g	Melanoma (2L)	NIV v IC	405 (63.5)	0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	<0.05
066 ^h	Melanoma (1L)	NIV v DAC	418 (47.8)	0.75 (0.55, 1.00)	NR	NE
KN-006 ⁱ	Melanoma (1L and 2L)	PEM v IPI	811 (NR)	0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS
				0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS
025 ^j	AMCCRCC (2L)	NIV v EVE	821 (60.5)	0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS
141 ^k	RMSCCHN (2L)	NIV v IC	361 (68.7)	0.75 (0.55, 1.00)	NR	NE
Meta-analysis – nivolumab in NSCLC (017, 057)				0.75 (0.55, 1.00) I ² =71.9%	0.75 (0.55, 1.00) I ² =0%	NS
Meta-analysis – PD pathway in NSCLC (017, 057, KN-010, OAK)				0.75 (0.55, 1.00)	0.75 (0.55, 1.00)	NS

Trial	Indication	Comparison	N (%) ^a	HR (95% CI) for OS		Test for interaction [*]
				<75 years	≥75 years	
				I ² =47.5%	I ² =0%	
	Nivolumab in melanoma (037)					<0.05
	Meta-analysis – PD pathway in melanoma (037, KN-006)			 I ² =64.8%	 I ² =0%	NS
	Meta-analysis – PD pathway in cancer (017, 057, KN-010, OAK, 025, 037, KN-006)			 I ² =49.9%	 I ² =0%	NS

AMCCRC=advanced or metastatic clear-cell renal cell carcinoma; ATE=atezolizumab; CI=confidence interval; DAC=dacarbazine; DOC=docetaxel; EVE=everolimus; HR=hazard ratio; IC=investigator choice; IPI=ipilimumab; NE=not estimable; NIV=nivolumab; NR=not reported; NS=not statistically significant at 5% level; NSCLC=non-small cell lung cancer; Non-Sq NSCLC=non-squamous non-small cell lung cancer; NR=not reported; PD-L1+=PD-L1 positive; PEM=pembrolizumab; RMSCCHN=recurrent or metastatic squamous cell carcinoma of the head and neck; Sq NSCLC=squamous non-small cell lung cancer; 1L=first-line; 2L=second-line.

Bold values indicate statistically significant differences

Additional meta-analyses conducted in StatsDirect and tests for interaction conducted during the evaluation (if not reported in the trial reports)

The results of the Keynote-024 trial were excluded from Table 3 and the meta-analyses as the estimates reported for subgroup analyses in Reck et al 2016 were for "Disease progression or death", rather than for death alone. For reference, the ITT HR (95% CI) for death = 0.60 (0.41, 0.89); ITT HR (95% CI) for disease progression or death = 0.50 (0.37, 0.68).

* approximated using a test for interaction relevant to relative risk estimates (<0.05 or NS)

^a N = total in trial and (%) = proportion aged <75years or <65 years (depending on the analysis)

^b pp11-12 of the minor re-submission and Figure 7.2.1-1, pp103-104 of the CA209-017 trial report. Minimum follow-up of 10.6 months.

^c pp11-12 of the minor re-submission and Figure 7.2.1-1, p124-126 of the CA209-057 trial report. Minimum follow-up of 13.2 months.

^d pp23-27 of the minor re-submission and Herbst et al 2016. Median follow-up was 13.1 months.

^e pp23-24 of the minor re-submission and Reck et al 2016. Median follow-up was 11.2 months. Comparator was investigators choice of one of the following five platinum-based chemotherapy regimens for 4 to 6 cycles: carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel. **Hazard ratio reported for disease progression OR death.** ITT HR (95% CI) for death =0.60 (0.41, 0.89); ITT HR (95% CI) for disease progression or death =0.50 (0.37, 0.68).

^f pp23-24 of the minor re-submission and Figure 3A, p9 of Rittmeyer et al 2016. Median follow-up of 21 months.

^g pp26-27 of the minor re-submission and Figure 7.3.1-1, pp106-107 of the CA209-037 trial report. Median follow-up was 15.34 and 13.67 months in the nivolumab and IC groups, respectively. Investigator's choice (IC) chemotherapy group: either dacarbazine (1000 mg/m² every three weeks [Q3W] or carboplatin AUC6 and paclitaxel 175 mg/m² Q3W). Subjects receiving IC were treated with a regimen which they had not previously received as therapy for metastatic melanoma.

^h pp26-27 of the minor re-submission and Figure 7.2.1-1, pp81-82 of the CA209-066 trial report. Median follow-up was not reported in the provided CSR.

ⁱ pp26-27 of the minor re-submission and Figure 2, p2526 of Robert et al 2015. Results reported for pembrolizumab 10 mg/kg q2w versus ipilimumab and pembrolizumab 10 mg/kg q3w versus ipilimumab (q2w reported first). Treated as two trials in the meta-analysis. Minimum follow-up was 12 months

^j pp26-27 of the minor re-submission and Figure 7.2.1-1, p117 of the CA209-025 trial report. Median follow-up 18.25 months for nivolumab and 17.22 months for everolimus.

^k pp26-27 of the minor re-submission and Figure 7.2.1-1, p84 of the CA209-141 trial report. Median follow-up 5.3 months for nivolumab and 4.5 months for investigators choice chemotherapy group. Investigator's choice therapy (cetuximab 400 mg/m² IV once, then 250 mg/m² weekly; methotrexate 40 mg/m² IV weekly, or docetaxel 30 mg/m² IV weekly).

6.27 The data from the individual trials indicated that:

- For those aged less than 75 years (reported in only Trial 017), a statistically significant improvement in overall survival was associated with treatment with nivolumab compared with docetaxel; and
- For those aged 75 or more (only reported in the nivolumab trials), there were no statistically significant differences between nivolumab or any comparator

(depending on indication) in any indication, with the exception of Trial CA209-066 (a comparison of nivolumab and dacarbazine in the treatment of first-line melanoma), which favoured nivolumab.

- 6.28 The data from the individual trials need to be interpreted in the context that very few patients (5-20%) aged 75 years or more were enrolled in the trials. Additionally, Brahmer et al (2015, publication of the CA209-017 trial) stated that the lack of treatment effect observed in those aged 75 years or more was “probably attributable to small sample sizes, a lack of adjustment of type I error for multiple comparisons, and an imbalance in ECOG performance-status score that favoured the docetaxel group in the subgroup of patients who were 75 years of age or older (in this subgroup, an ECOG performance-status score of 1 was assessed in 91% of the patients in the nivolumab group, vs. 61% of those in the docetaxel group)”; noting that the trial enrolled those with an ECOG performance-status of 0 or 1.
- 6.29 The meta-analyses conducted for those aged 75 years or more indicated:
- there was significant heterogeneity observed for all analyses indicating likely inappropriate combination of trial results; and
 - no differences between nivolumab and its comparators in terms of overall survival in the treatment of NSCLC, melanoma or “cancer” were observed.
- 6.30 The test for interaction (comparing those aged less than 75 years and those aged 75 years or more) indicated that age was a treatment effect modifier for nivolumab in the treatment of NSCLC from data reported in Trial CA209-017.
- 6.31 Given the relatively small number of patients informing the comparative effect of nivolumab compared with its comparator in NSCLC among those aged 75 years or more in Trial CA209-017 (n=11 and 18 in the nivolumab and docetaxel treatment groups, respectively), a comparison of those aged less than 75 years from Trial CA209-017 (n=124 for nivolumab and n=119 for docetaxel) and a meta-analyses of those aged 75 years or more from all NSCLC (n=31 for nivolumab and n=41 for docetaxel) or all cancer trials (n=144 for nivolumab and n=143 for the comparator) was also conducted. The test for interaction continued to indicate age was a treatment effect modifier with the inclusion of data from the other NSCLC trial (CA209-057), however this effect was no longer observed upon inclusion of the melanoma (CA209-037, -066) and other cancer (CA209-025) trials.
- 6.32 Given many of the trials reported overall survival in both the less than 65 years and 65 years or more subgroups, these were provided for information purposes only. The results of this analysis demonstrated that:
- variable results were observed, with some trials reporting statistically significant improvements in overall survival for the treatment compared with the comparator amongst those aged less than 65 years, but not those aged 65 years or more (or vice versa), with other trials reporting differences in both groups or no differences in both groups.
 - the test for interaction (comparing those aged less than 65 years and those aged 65 years or more) indicated that age was only a treatment effect modifier for nivolumab in the treatment of melanoma from data reported in Trial CA209-037, with treatment effects being greater in the older sub-group. This needs to be interpreted in the context that no significant differences in overall survival were

reported for the ITT population of Trial CA209-037, and the conduct of subsequent subgroup analyses was questionable. This was also in contrast to the results reported for age as a treatment effect modifier among those aged less than 75 years or 75 years or more among those with NSCLC.

- 6.33 The minor re-submission also presented data reported in the single-arm studies of nivolumab in the treatment of NSCLC, CHECKMATE-153 (squamous and non-squamous), the Italian Expanded Access Program (EAP; squamous) and the BMS Australian named patient program (BMSA NPP; squamous and non-squamous).
- 6.34 The results reported in CHECKMATE-153, presented at the 17th World Conference on Lung Cancer; based on those aged less than 70 years and 70 years or more and those with an ECOG performance-status of 0-1 or 2, demonstrated that, while the estimated 6-month and 1-year overall survival rates were comparable across the age subgroups of those aged less than 70 years and 70 years or more, the estimated 6-month and 1-year OS rates in the ECOG performance-status 2 subgroup were lower than those in the ECOG performance-status 0-1 subgroup. This supports the authors of the publication of Trial CA209-017 (Brahmer et al 2015) in their contention that a potential reason for the observed lack of effect among those aged 75 years or more in the trial may have been due to ECOG performance-status rather than age (see paragraph 6.28 above). The PBAC considered that it was possible that poor performance status might also predict poorer response to nivolumab, but noting that older patients generally have a lower performance status, it may not be straightforward to determine the best basis for prediction. For this reason, the PBAC reemphasised that any restriction for nivolumab should be limited to a WHO performance status of 0 or 1.
- 6.35 Further analysis of the CHECKMATE-153 study, presented by the sponsor for the purposes of its minor re-submission, to those aged 75 years and more are presented in Figure 1 and Table 6.

Figure 1: Overall survival reported in CHECKMATE-153 for those aged ≥ 75 years, by ECOG performance-status



Table 6: Median overall survival reported for those aged ≥75 years, with an ECOG performance-status of 0, 1 or 2 observed in CHECKMATE-153

Age/ECOG performance-status	Median overall survival, months
≥75 years, ECOG 0 (n=46)	
≥75 years, ECOG 1 (n=199)	
≥75 years, ECOG 2 (n=32)	

Source: pp15-16 of the minor re-submission

- 6.36 No data regarding the treatment effect observed in the entire population or in the complement group (ie, those aged less than 75 years) from CHECKMATE-153 were provided to allow for a comparison. However, as discussed in paragraph 6.28 above, and based on the data reported in Table 6, ECOG performance-status appeared to be driving the observed lack of effect in those aged 75 years or more.

6.37 The results reported for the Italian EAP are presented in Table 7 and Figure 2.

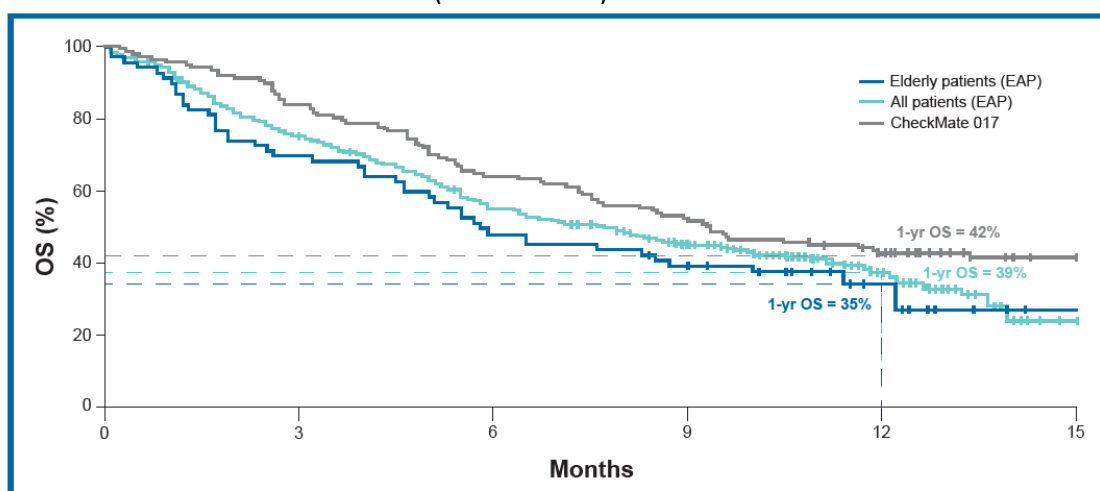
Table 7: Results for those aged ≥75 years and all patients in the Italian EAP

Response	Aged ≥75 years (n=70)		All patients (n=371)	
	First tumour assessment	Best response	First tumour assessment	Best response
Overall response rate, n (%)	8 (11)	13 (19)	51 (14)	67 (18)
Disease control rate, n (%)	25 (36)	30 (43)	151 (41)	175 (47)
Overall response, n (%)				
Complete response, n (%)	0	0	1 (<1)	4 (1)
Partial response, n (%)	8 (11)	13 (19)	50 (14)	63 (17)
Stable disease, n (%)	17 (25)	17 (24)	100 (27)	108 (29)
Progressive disease, n (%)	43 (61)	38 (54)	212 (57)	189 (51)
Not determined, n (%)	2 (3)	2 (3)	8 (2)	7 (2)

Source: Table 6, p17 of the minor re-submission

6.38 Comparable overall response and disease control rates were observed amongst those aged 75 years or more and the entire population enrolled in the Italian EAP.

Figure 2: Overall survival reported for those aged ≥75 years and all patients in the Italian EAP and those treated with nivolumab in Trial CA209-017 (Checkmate 017)



Source: Figure 4, p18 of the minor re-submission

6.39 In terms of overall survival (Figure 2), the effect of nivolumab therapy was lower among those aged 75 years or more compared with the entire population in the Italian EAP. Both these results were less compared with those treated with nivolumab in Trial CA209-017 with 1-year overall survival rates of 35% for Italian EAP patients aged 75 years or more, 39% for Italian EAP entire population and 42% for those treated with nivolumab in Trial CA209-017.

6.40 The minor re-submission also presented data from the BMSA NPP. There was insufficient data provided in the minor re-submission to assess whether those enrolled in this program would be eligible for nivolumab under the requested restriction. Results of the BMSA NPP regarding duration of therapy across age groups indicated that the average duration of therapy in patients aged less than 75 years was [redacted] days (SD [redacted] days) compared to the average duration of therapy

in patients aged 75 years or more being [REDACTED] days (SD [REDACTED] days). The minor re-submission stated that “notwithstanding caveats about using duration of therapy as a surrogate for survival, the results from the Australian NPP should provide the PBAC further confidence regarding nivolumab effectiveness in NSCLC patients [aged 75 years or more].”

- 6.41 The minor re-submission claimed that the results of the meta-analysis of Trials CA209-017 and -057 demonstrate that patients aged 75 years or more derive a similar efficacy benefit compared with docetaxel. Although no statistically differences were reported (HR=1.23; 95% CI: 0.66, 2.31), there is still an increased risk of death associated with treatment with nivolumab compared with docetaxel, despite the accepted superiority claim with respect to safety. Additionally, the test for interaction demonstrated that age was a treatment effect modifier in the analysis of the CA209-017 trial alone and when both sub-groups aged 75 years or more from Trials CA209-017 and -057 were combined and compared against those aged less than 75 years in the CA209-017 trial. CHECKMATE-153 provided little additional data as no overall survival estimates were provided regarding the treatment effect observed in the entire population or in the complement group (ie, those aged less than 75 years) to allow for a comparison, although data reported based on ECOG performance-status indicated worse ECOG performance-status was likely driving the lack of observed benefit from nivolumab. The Italian EAP reported 1-year overall survival rates: 35% for Italian EAP aged 75 years or more and 39% for Italian EAP entire population compared with 42% for those treated with nivolumab in Trial CA209-017; these data need to be interpreted bearing in mind the observational nature of the study.
- 6.42 In the meta-analysis of NSCLC pembrolizumab and atezolizumab trials, variable results were observed. Some trials reporting statistically significant improvements in overall survival for the treatment compared with the comparator amongst those aged less than 65 years, but not those aged 65 years or more (or vice versa), with other trials reporting differences in both groups or no differences in both groups. Age was not demonstrated to be a treatment effect modifier when separating patients based on ages less than 65 and 65 years or more (except in Trial CA209-037, where no differences were observed in the ITT population and thus sub-group analysis was likely inappropriate).
- 6.43 Based on the PD pathway trials in other indications, the only inconsistency across nivolumab trials observed with regard to efficacy in patients aged 75 years or more was Trial CA209-066 demonstrating a statistically significant improvement in overall survival compared with dacarbazine. All other trials demonstrated no statistically significant differences and given all but Trial CA209-037 demonstrated statically significantly improved survival in the ITT population, this must have been driven by those aged less than 75 years (results were not reported for this sub-group by most trials), indicating age may be a potential prognostic factor.
- 6.44 The PBAC considered that the meta-analyses presented of randomised trials of nivolumab, in both NSCLC alone and combined with other cancers, did not adequately resolve the uncertainties regarding the comparative effectiveness of nivolumab in patients 75 years or older. The PBAC considered that the other analyses presented were less informative.

Proposed Managed Entry Scheme - (patients aged 75 years or older)

6.45 The minor re-submission stated that there are practical challenges associated with potential future data becoming available which makes defining a MES based on age difficult and that it is unlikely that additional meaningful evidence will become available. Specifically:

- **Future nivolumab data in NSCLC** - a review of the sponsor's internal database identified two phase III nivolumab monotherapy NSCLC trials (CA209-026 [first-line NSCLC that did not meet the primary endpoint] and -227 [first-line NSCLC not fully reporting until ██████████]). The sponsor stated that it does not believe that data from either of these two nivolumab trials will provide any better evidence than currently available with respect to effectiveness of nivolumab in patients aged 75 years or older.
- **Future PD-pathway data in NSCLC** – currently published trial results report subgroup analyses of age by less than 65 years and 65 years or older. The minor re-submission stated that this is unlikely to change in the future, and as such, the sponsor believes future PD NSCLC trial data will not assist with the research question regarding treatment effect among those aged 75 years or older.
- **Future PD-pathway data (including nivolumab in other cancer types)** – the minor re-submission stated there are multiple nivolumab phase III clinical trials planned in non-NSCLC indications, the vast majority are single arm or non-comparative as they are in smaller cancer indications with limited treatment options. The minor re-submission also cited that as for “Future PD-pathway data in NSCLC” above, other PD-pathway treatments are unlikely to report efficacy data in the required age group. As such, the minor re-submission stated that the sponsor does not believe that future PD data specific to other cancer types will provide any better evidence than currently available with respect to effectiveness of nivolumab in patients aged 75 years or older with lung cancer.

6.46 The PBAC considered that the challenges raised by the submission regarding an MES to address the uncertainty relating to patients aged 75 years or older meant that other avenues to address the implications of this uncertainty should be explored.

Proposed Risk Sharing Arrangement – Age (an alternative to a Managed Entry Scheme)

6.47 The sponsor reiterated that the evidence presented in the minor re-submission demonstrates the effectiveness of nivolumab in patients 75 years or older with an ECOG performance-status of 0 to 1. However, the minor re-submission proposed an alternative to an MES (an RSA) if the PBAC does not consider that the age question has been adequately resolved:

- A rebate for greater than expected use in older patients, that being use in more than █████% of patients aged 75 years or older, with the minor re-submission suggesting that greater than expected use is attributable to patients with an ECOG performance-status>1 (i.e. use outside the proposed PBS restriction). The minor re-submission derived the figure of █████% from the █████% of patients with squamous NSCLC currently 75 years or older with an ECOG performance-status of 0-1 that were treated on the Patient Access Program, and allowing for natural variability. As the minor re-submission stated that █████% of patients with non-squamous NSCLC from the Patient Access Program were 75 years or older with

an ECOG performance-status of 0-1, it was not clear why the higher rate of █% of patients 75 years or older with squamous NSCLC was chosen rather than the weighted average figure of █%.

- The rebate would consist of:
 - █% being paid to the Commonwealth from the sponsor for use in more than █% up to █% of patients aged 75 years or older at initiation of nivolumab. This proposed range of █% to █% is arbitrarily assigned and inconsistent with █% of patients 75 years or older with non-squamous NSCLC.
 - A rebate for use in greater than █% of patients calculated so that the effective price for those patients was equivalent to the comparator price (docetaxel for squamous NSCLC and █% docetaxel and █% pemetrexed for non-squamous cell NSCLC). The assumed proportion of █% docetaxel and █% pemetrexed was inconsistent with the PBAC's assertion that pemetrexed should be the main comparator for non-squamous NSCLC in this population. The justification for the nominated proportion between docetaxel and pemetrexed was unclear.
- Only Commonwealth expenditure post-rebate specific to the percentage of patients 75 years or older above the base level of █% to be included in the broader RSA cap calculations proposed in the RSA. Practically, the age base rebate would be calculated first and any rebate payable would be deducted from the total patient cap rebate so as not to double count the rebates.

6.48 The pre-PBAC response proposed a revised RSA for age with a threshold of █% and rebate for any patient 75 years or older above this threshold down to a weighted comparator price of docetaxel (for squamous NSCLC) and pemetrexed (for non-squamous NSCLC). The PBAC noted that this was higher than the proportion of patients in the NPP who were 75 years or older with an ECOG performance status of 0-1, but accepted the proposed threshold of █%.

- 6.49 In relation to administrative considerations, the minor re-submission proposed that:
- the Department could capture age upon initiation data, and that the sponsor would also look to independently validate this. Medicare claims data would be a reliable source regarding age of patients at initiation of treatment with nivolumab and no further specific data gathering would be required;
 - a significant body of data be collected before an invoice for the rebate was triggered, although the minor re-submission noted that results would be applied retrospectively from Day 1 of PBS listing. The PBAC noted that RSAs are generally invoiced annually, and this would also be required in practice in this case, in order to align with the financial cap reconciliation;
 - re-negotiation of the agreement if there is a disproportional change in the number of elderly NSCLC patients being initiated in the second-line setting. The PBAC did not accept this proposal, given that the proposed RSA is specifically designed to address the risk that this might occur and it was therefore unclear what change the sponsor might consider would trigger a renegotiation; and
 - a lapsing of the agreement if data over the first 2-3 years of PBS listing indicates that the proportion of patients 75 years or older falls well below the estimated base level. The PBAC considered that this was a matter for negotiation with the Department. As a matter of practice, Deeds containing RSAs are negotiated for a period of 5 years.

- 6.50 The PBAC provided the following comments in relation to the ICERs presented in the major re-submissions at the November 2016 meeting:
- i) \$45,000 - \$75,000/QALY for squamous NSCLC versus docetaxel; considered to be high and an underestimate of the true ICER as a result of optimistic assumptions considered favourable to nivolumab particularly regarding methods of extrapolation and the time horizon (paragraph 7.8, 7.06 nivolumab PSD, November 2016); and
 - ii) \$75,000 - \$105,000/QALY for non-squamous NSCLC versus docetaxel (presented in the Pre-PBAC response to the re-submission considered at the November 2016 PBAC meeting); considered to be high and an underestimate of the true ICER as a result of optimistic assumptions considered favourable to nivolumab particularly regarding methods of extrapolation and the time horizon (paragraph 7.10, 7.07 nivolumab PSD, November 2016); or
 - iii) \$15,000 - \$45,000/QALY for non-squamous NSCLC versus pemetrexed (presented in the Pre-PBAC response to the re-submission considered at the November 2016 PBAC meeting); where the PBAC considered that base case ICER of \$45,000 - \$75,000/QALY in the re-submission considered at the November 2016 meeting could not be relied upon given the concerns regarding the validity of the indirect comparison of nivolumab vs. pemetrexed (paragraphs 7.10 and 7.11, 7.07 nivolumab PSD, November 2016).
- 6.51 Alternative approaches to provide the PBAC with assurance that the ICERs estimated in the major re-submissions considered at the November 2016 PBAC meeting are achieved were:
- that the cost of nivolumab should not exceed that of the comparators for the proportion of patients aged 75 years or older as enrolled in the trials (10.7% in Trial CA209-017 [squamous NSCLC] and 7.4% in Trial CA209-057 [non-squamous NSCLC]), as the economic evaluations were presumably based on the ITT populations; or
 - that the cost of nivolumab not exceed the cost of the comparators for all patients aged 75 years or older as the minor re-submission states that “patients aged 75 years or older derive a similar efficacy benefit compared with docetaxel”.
- 6.52 The PBAC considered that the proposed RSA for patients aged 75 years or older as defined in paragraph 6.48 would adequately address concerns regarding the comparative effectiveness of nivolumab in patients 75 years or older.

Economic analysis

- 6.53 As a minor submission, there was no economic comparison presented.

Estimated PBS usage & financial implications

- 6.54 The minor re-submission proposed an RSA which capped the average number of administrations per patient per year at ■■■, in line with the PBAC PSDs from the November 2016 meeting (paragraph 7.9, 7.06 nivolumab PSD and paragraph 7.11, 7.07 nivolumab PSD, November 2016). With a capped average administration of ■■■ infusions per patient per year, the minor re-submission estimated a net cost to the PBS of more than \$100 million in Year 5 of listing, with a total net cost to the PBS of \$more than 100 million over the first 5 years of listing. Further details on the estimated PBS usage and financial implications are outlined below under 'Risk Sharing Arrangements'.

Risk Sharing Arrangements

- 6.55 The minor re-submission noted that the proposed RSA was not intended to be a complete and final RSA.
- 6.56 The minor re-submission used a stepwise approach to develop an expenditure cap, which it stated could be improved upon in discussions with the Department. The stepwise approach was based upon:
- limiting the total cost per patient to an ex-manufacturer cost of \$■■■■■■■■■■, based on an average of ■■■ infusions per patient per year with a dose of 2 x 100 mg vials and 1 x 40 mg vials;
 - limiting patient numbers, after increasing the uptake rate for both squamous and non-squamous indications by ■■■%. The rationale for the increasing uptake rate assumption by ■■■% was not provided in the minor re-submission, although the minor re-submission stated that this was conservative;
 - adjusting to account for a short duration of therapy for some patients in Year 1 of listing, due to commencement of therapy later in the year of listing (a rolling approach was used to estimate prescription numbers for patients initiating treatment in months 8 through to 12). If this adjustment is applied to all new patients, it should also be applied to grandfathered patients (noting that grandfather patients should receive a minimum of 1 and a maximum of 11 PBS-subsidised cycles); and
 - including less than 10,000 grandfathered patients in Year 1 of listing in the financial estimates, but excluding these from the proposed RSA (see Table 8 below). However, the PBAC considered that it would be inappropriate for the grandfathered patients who meet the restriction to be excluded from the RSA.
- 6.57 The minor re-submission proposed that should the cost to the PBS exceed the estimates presented, that a rebate of 100% of the expenditure above the estimated caps should apply, with the rebate not applying to grandfathered patients. It is not appropriate to exclude grandfathered patients from the proposed RSA. The PBAC recommended that the number of grandfathered patients should be included in the cap estimates.
- 6.58 Patient numbers and the maximum cost to the PBS under the proposed RSA in the minor re-submission are presented in Table 8.

Table 8: Patient numbers including dose-adjustment and grandfathering

	Year 1*	Year 2	Year 3	Year 4	Year 5
Patient numbers (including grandfathering)					
Squamous NSCLC patients receiving nivolumab	█	█	█	█	█
Non-squamous NSCLC patients receiving nivolumab	█	█	█	█	█
TOTAL SQ + NSQ	█	█	█	█	█
Maximum cost to the PBS for nivolumab under the proposed risk sharing arrangement, including grandfathered patients**					
Squamous NSCLC	\$ █	\$ █	\$ █	\$ █	\$ █
Non-squamous NSCLC	\$ █	\$ █	\$ █	\$ █	\$ █
TOTAL SQ + NSQ NSCLC	\$ █	\$ █	\$ █	\$ █	\$ █
Maximum cost to the PBS for nivolumab under the proposed risk sharing arrangement, excluding grandfathered patients**					
Squamous NSCLC	\$ █	\$ █	\$ █	\$ █	\$ █
Non-squamous NSCLC	\$ █	\$ █	\$ █	\$ █	\$ █
TOTAL SQ + NSQ NSCLC	\$ █	\$ █	\$ █	\$ █	\$ █

SQ=squamous cell; NSQ=non-squamous cell; NSCLC=non-small cell lung cancer

* Estimates included █ grandfathered patients in Year 1 of listing (█ squamous cell NSCLC patients and █ non-squamous cell NSCLC patients)

** Costs based on dispensed price for maximum amount, minus co-payments

Source: Table 19, p56, Table 20, p57 and of the minor submission and Attachment 2 and 3 MS Excel workbooks, provided with the minor submission

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

- 6.59 The minor re-submission's approach to dose uptake was reasonable, and while some effect in Year 2 would also be expected, the effect in Year 1 would be most significant. While the March 2016 submission included an allowance for less than 10,000 grandfathered patients, the minor re-submission increased the number of grandfathered patients to less than 10,000 based on increased numbers of patients in the Patient Access Program which commenced upon the TGA registration of nivolumab. Including an allowance for a higher number of grandfathered patients was appropriate. However, the basis for estimating less than 10,000 or the less than 10,000 patients currently on the program was unclear. The minor re-submission stated that currently less than 10,000 patients are supported in the sponsor's Patient Access Program. The minor re-submission stated that the sponsor has proposed that the grandfathering cap be set to less than 10,000 (less than 10,000 squamous NSCLC patients and less than 10,000 non-squamous NSCLC patients) patients and these grandfathered patients are all to be transitioned in the first year of PBS listing. The PBAC noted that, as proposed in the submission, the grandfather patients were not incorporated into the dosing cap adjustment. These patients should be introduced with a variable number of infusions, applying the same methodology as proposed for the dose uptake adjustment and be limited to █ infusions.
- 6.60 Overall, the minor re-submission stated that the RSA proposed would reduce the maximum cost to the PBS for nivolumab by \$60 - \$100 million over 5 years compared to that presented in the November 2016 re-submissions. The PBAC noted that savings compared to the previous re-submissions were primarily due to limiting

the nivolumab per patient cost for RSA and ICER purposes to ■ infusions per patient per year.

- 6.61 The PBAC advised that grandfathered patients should be included in the overall patient count for the RSA. The PBAC advised that the RSA should take into account that these patients would already have received a variable number of doses under the Patient Access Program, and should therefore have the same dose adjustment applied as standard patients to a maximum of ■ PBS subsidised infusions.
- 6.62 The PBAC advised that its previous concerns with the ability of the proposed RSA to achieve its intended purposes were now allayed because the total patient pool and the dose-adjusted maximum duration of treatment and hence the cost per patient were now clearly articulated, and the further dose adjustments offered in the revised RSA proposal satisfactorily accounted for the lags which were the source of the PBAC's previous concerns. In addition, the PBAC advised that corresponding adjustments should also apply to ensure the appropriate inclusion of grandfathered patients. The PBAC further advised that the proposed RSA with an overall cap on patient numbers receiving nivolumab for NSCLC and cost per patient of nivolumab in NSCLC (to ensure that the estimated ICER is not exceeded) and 100% rebate for utilisation over the caps would also adequately address concerns of use outside the restriction and uncertainty around treatment duration. The PBAC then advised that the Department and sponsor ensure that the merging of this RSA with the subsequently proposed RSA to manage uncertainty related to the effectiveness of nivolumab in patients 75 years or older be achieved in such a way that both RSAs achieve all their objectives.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of nivolumab for the treatment of locally advanced or metastatic, squamous or non-squamous, non-small cell lung cancer (NSCLC). The PBAC considered that, with its suggested modifications, the risk sharing arrangements proposed by the sponsor adequately addressed concerns regarding the possible variation in the extent of effectiveness in patients 75 years or older, and uncertainties regarding the ICERs presented in the November 2016 submissions, the overall numbers using nivolumab in NSCLC, the risk of leakage of nivolumab outside of the intended restriction, and the duration of nivolumab treatment.
- 7.2 The PBAC reiterated its view that there is a clinical need for new treatments for patients with squamous and non-squamous NSCLC.
- 7.3 The PBAC noted that the meta-analyses of pre-defined subgroups (based on PD-L1 expression) of the nivolumab trials presented did not indicate a clear prediction by PD-L1 status on the comparative effectiveness of nivolumab. The PBAC therefore considered that it would be appropriate to provide nivolumab to a broad population of patients irrespective of PD-L1 status, with reporting on biomarker status evidence updated to the PBAC by the sponsor in a new submission if this conclusion should be modified. The PBAC requested that the sponsor provide more information on the

ability to conduct further post hoc analyses on stored samples from trial participants in previous and current trials if a new potential biomarker emerges. The PBAC therefore recommended that if a biomarker that did predict treatment effect modification was identified, the sponsor would be required to make a new submission to the PBAC (and MSAC if applicable).

- 7.4 The PBAC considered the potential consequences for any new submission could include:
- i) If a subgroup with a better outcome was identified – no increase to the price of nivolumab may be warranted;
 - ii) If a subgroup with no effect or a worse outcome was identified – the restriction should be narrowed to exclude these patients from PBS subsidised treatment. There would be no retrospective rebate requested for these patients, however the RSA would be adjusted accordingly to account for the exclusion of these patients.
- 7.5 The PBAC noted that the meta-analyses of randomised trials of nivolumab in NSCLC, and in NSCLC, melanoma and renal cell carcinoma combined, both indicated no significant improvement in overall survival associated with treatment with nivolumab over standard chemotherapy for the subgroups of patients aged 75 years or older. The PBAC noted that the meta-analyses of randomised trials of any anti-PD1 therapy across cancers indicated significant improvement in overall survival associated with treatment with anti-PD1 therapy over standard chemotherapy for the subgroup of patients aged 65 years or older, but considered that this redefined included mostly patients aged less than 75 years and so was less informative. The PBAC noted that the subgroup analyses of other nonrandomised studies presented in the minor resubmission were also less informative because they did not report comparative outcomes for nivolumab over standard chemotherapy. Overall, although the PBAC acknowledged that the meta-analysis of nivolumab NSCLC trials were underpowered due to the small number of patients aged 75 years or older, the PBAC reiterated its previous concern about the incremental effectiveness of nivolumab in patients 75 years or older.
- 7.6 The PBAC agreed with the submission that there were practical challenges that would limit the value of a managed entry scheme (MES) to address the uncertainty regarding age as a treatment effect modifier in nivolumab treatment. However, the PBAC considered that the proposed risk sharing arrangement (RSA) for patients aged 75 years or older would adequately address these concerns. The PBAC recommended that the limit for the proportion of patients aged 75 years or older in calculating the RSA caps should be ██████%.
- 7.7 The PBAC reiterated that, in addition to the RSA for patient age, an RSA providing an overall cap on patient numbers and the more appropriate dose-adjusted cost per patient with 100% rebate for utilisation over the caps would be required to address the concerns with use outside the restriction and uncertainty around treatment duration. The PBAC also advised the proposal to limit the total cost per patient should also apply to grandfathered patients (see paragraphs 6.57, 6.61 and 6.62).
- 7.8 The PBAC advised that patients should only be eligible for access to PBS subsidy through the grandfather restriction if they have an ECOG performance-status of 0 or 1 and have stable or responding disease. The PBAC noted that the number of patients with an ECOG performance-status of 0-1 on the sponsor's Patient Access

Program was currently unclear and recommended that the Department and sponsor hold further discussions to agree on a practical approach to identify the number of these patients.

- 7.9 In making this recommendation, the PBAC noted that the grandfather restriction for nivolumab for unresectable Stage III or Stage IV malignant melanoma has been PBS listed for almost a year and hence should be removed. The PBAC also recommended that the Administrative Advice in the initial treatment restriction should be based on that for nivolumab in melanoma to recommend a repeat scan at least 4 weeks after suspected pseudo-progression. The PBAC recommended that patients should only continue on PBS subsidised treatment if they have stable or responding disease.
- 7.10 The PBAC advised that nivolumab should be exempt from the Early Supply Rule as it currently does not apply to Section 100 Efficient Funding of Chemotherapy listings.
- 7.11 The PBAC advised that nivolumab is not suitable for prescribing by nurse practitioners.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	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	8	Opdivo® Bristol-Myers Squibb Australia Pty Ltd (BQ)

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-small cell lung cancer
PBS Indication:	Locally advanced or metastatic non-small cell lung cancer
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:	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 treatment for this condition AND The condition must have progressed on or after prior platinum based chemotherapy.
Prescriber Instructions:	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice:	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. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	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	11	Opdivo® Bristol-Myers Squibb Australia Pty Ltd (BQ)

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-small cell lung cancer
PBS Indication:	Locally advanced or metastatic non-small cell lung cancer
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 received PBS-subsidised treatment with this drug for this condition AND The treatment must be the sole PBS-subsidised treatment for this condition AND Patient must have stable or responding disease.
Administrative Advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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-small cell lung cancer
PBS Indication:	Locally advanced or metastatic non-small cell lung cancer
Treatment phase:	Grandfathering 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 received treatment with this drug for this condition prior to <listing date> AND The treatment must be the sole PBS-subsidised treatment for this condition AND Patient must have stable or responding disease AND Patient must have a WHO performance status of 0 or 1
Prescriber Instructions	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
Administrative Advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

9 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.

10 Sponsor's Comment

The sponsor acknowledges the collaborative work of all stakeholders pre and post the positive PBAC recommendation and looks forward to eligible Australian patients being able to access nivolumab via the PBS in the near future.