

**7.09 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

- 1.1 The early re-entry resubmission sought a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for nivolumab in combination with chemotherapy for the neoadjuvant treatment of patients with resectable non-small cell lung cancer (NSCLC).
- 1.2 The resubmission was based on the PBAC decision to not recommend nivolumab for this indication from March 2023. Table 1 outlines the issues raised by the PBAC in March 2023 and how these issues were addressed in the resubmission.

Table 1: Summary of key matters to be addressed

Matter of concern	Response	Addressed?
Revision to the proposed restriction		
There was inadequate evidence provided in the submission to support Scenario 1 (a listing agnostic to EGFR and ALK status) and considered that Scenario 2 (a listing that excludes patients with known sensitising EGFR mutations or ALK alterations) would be consistent with the pivotal clinical trial and the proposed TGA restriction. The PBAC therefore considered that Scenario 2 was the appropriate listing scenario for nivolumab (paras 7.3 and 7.21).	The resubmission proposed a listing that excluded patients with known sensitising EGFR mutations or ALK alterations.	Yes
Revision of inputs to the economic evaluation		
<u>Time horizon of 15 years</u> The PBAC considered the short follow-up of the CM816 trial (median: 29.5 months) did not provide a reliable basis for the extrapolation of outcomes over a 25 year model time horizon. The PBAC considered that based on the duration of follow-up in the clinical trial and the associated immature OS data, a 15-year time horizon was more reasonable. However, the PBAC also noted that due to one-off costs and outcomes being applied in the DM health state reducing the time horizon did not address uncertainties related to this health state (paras 7.14 and 7.21).	A time horizon of 15 years was applied to the economic evaluation.	Yes
<u>Onset of cure of 6 years in the neoNIVO+neoChemo arm</u> The economic model allowed a proportion of patients in the EFS health state who are 'cured' to increase linearly from Year 5 to a maximum of 95% at Year 7 in both arms of the model. In the context of limited data to support the cure assumptions for neoNIVO+neoCHEMO, the PBAC advised that it would be more appropriate for the onset of cure to be delayed from 5 years to 6 years in the neoNIVO+neoCHEMO arm of the economic model (paras 7.15 and 7.21).	The onset of cure was delayed to 6 years in both treatment arms rather than in the neoNIVO+neoChemo arm only.	Unclear

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Matter of concern	Response	Addressed?
<p><u>EFS and LR health state utilities</u> The utility value for EFS, based on the EQ-5D data from the CM816 trial, was higher than the expected utility for the general Australian population (0.874 vs. 0.850) and therefore the general population utility of 0.850 was used for EFS. This resulted in an assumption of no QoL decrements associated with a diagnosis of NSCLC or its treatment in the economic model. The PBAC considered a decrement in QoL should be modelled and that the use of health-state utilities from Grutters et al 2010 would be more clinically appropriate (paras 7.16 and 7.21).</p>	<p>The EFS and LR health state utilities from Grutters et al 2010 was applied to the economic model.</p>	<p>Yes</p>
<p><u>Price reduction</u> The PBAC considered that with the required revisions to the model inputs (noted above) a price reduction would be required for nivolumab to be considered cost-effective in the neoadjuvant NSCLC setting, i.e. an ICER of no more than \$30,000 per QALY gained (paras 7.18 and 7.21).</p>	<p>The effective EMP in the resubmission of \$ [REDACTED] per 100 mg vial is 34.2% lower than the \$ [REDACTED] per 100 mg vial proposed in the March 2023 submission.</p> <p>The re-specified base case ICER presented in the resubmission was \$ [REDACTED]¹ per QALY gained. However, the ICER increased to \$ [REDACTED]¹ per QALY gained if an onset of cure of 5 years is retained in the neoChemo arm.</p>	<p>Unclear</p>
Revision of inputs to the financial estimates		
<p><u>Cost offsets</u> The PBAC noted the only cost-offsets considered in the financial estimates related to the use of chemotherapy. The PBAC considered cost-offsets associated with reduced use of adjuvant atezolizumab, durvalumab in borderline resectable stage III NSCLC and immunotherapy for metastatic disease should be accounted for in any revised estimates (paras 7.19 and 7.21).</p>	<p>The revised financial estimates included cost-offsets associated with the reduced use of adjuvant atezolizumab, durvalumab in borderline resectable stage III NSCLC and immunotherapy for metastatic disease. However, the patient numbers increased compared with the March 2023 submission. An epidemiological approach rather than a market share approach was used to estimate offsets.</p>	<p>Unclear</p>
<p><u>Revision to price of nivolumab</u> The PBAC considered that any revised financial estimates should include recalculation using a revised neoadjuvant nivolumab price (para 7.21).</p>	<p>The revised financial estimates included the revised neoadjuvant nivolumab price. However, a further price reduction would be required to achieve an ICER of not more than \$30,000 per QALY gained if amendments to the onset of cure assumptions in the base case of the economic model are required.</p>	<p>Unclear</p>

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Matter of concern	Response	Addressed?
RSA across immunotherapies in NSCLC		
<p>The PBAC considered that it would be appropriate for nivolumab to be included in the current RSA in place for immunotherapies for NSCLC. The PBAC further considered it would be appropriate to manage the uncertainties associated with retreatment with immunotherapy in metastatic disease within the RSA, given there is no clinical data to support such use.</p> <p>The PBAC considered an early re-entry resubmission should include proposed parameters for revising the current RSA in place for immunotherapies for NSCLC to include neoadjuvant nivolumab (paras 7.20 and 7.21).</p>	<p>The resubmission did not include proposed parameters for revising the current RSA in place for immunotherapies for NSCLC to include neoadjuvant nivolumab.</p> <p>The resubmission stated the sponsor is willing to negotiate increased financial caps. However, the sponsor requested that the requirement for an RSA and negotiated increase in financial caps be reassessed in consideration of the overall net cost to the PBS/RPBS calculated using effective prices for adjuvant atezolizumab, durvalumab and metastatic pembrolizumab (current estimates apply published prices).</p>	<p>No</p>

Source: 6.06 nivolumab PBAC Public Summary Document (PSD), March 2023 PBAC meeting.

ALK = anaplastic lymphoma kinase; DM = distant metastasis; EFS = event-free survival; EGFR = epidermal growth factor receptor; EMP = ex-manufacturer price; neoNIVO+neoChemo = nivolumab (360 mg intravenous [IV] Q3W for a maximum of 3 cycles) plus platinum-doublet chemotherapy; LR = locoregional recurrence; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life year; QoL = quality of life; RSA = risk sharing agreement.

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$35,000 to < \$45,000

2 Background

- 2.1 Nivolumab was TGA registered on 20 February 2023 for the following indication:

“OPDIVO, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of patients with resectable non-small cell lung cancer (NSCLC).”
- 2.2 Nivolumab is currently TGA-approved as an adjuvant treatment for several other types of cancer, including resectable/resected melanoma, urothelial carcinoma, oesophageal cancer and gastro-oesophageal junction cancer.
- 2.3 The PICO from the previous submission is presented below.

Table 2: Key components of the clinical issue addressed by the submission (as stated in the March 2023 submission)

Component	Description
Population	Patients with resectable (tumours \geq 4 cm or node positive) NSCLC
Intervention	Nivolumab, 360 mg Q3W plus chemotherapy Q3W
Comparators	Main: Neoadjuvant chemotherapy Additional: <ul style="list-style-type: none"> Adjuvant chemotherapy Adjuvant chemotherapy followed by atezolizumab
Outcomes	Primary: EFS Key secondary: OS, TTDM, HRQoL, pCR, MPR, safety
Clinical claim ^a	Compared to neoadjuvant chemotherapy, neoadjuvant nivolumab plus chemotherapy has superior comparative efficacy and non-inferior safety. Compared to adjuvant chemotherapy, neoadjuvant nivolumab plus chemotherapy has superior comparative efficacy and non-inferior safety. Compared to adjuvant chemotherapy followed by atezolizumab, neoadjuvant nivolumab plus chemotherapy has 'likely superior and at least non-inferior' comparative efficacy and 'different and non-inferior' safety.

Source: Table 2, p21 of the March 2023 submission.

EFS = event-free survival; HRQoL = health-related quality of life; MPR = major pathologic response; NSCLC = non-small cell lung cancer; OS = overall survival; pCR = pathologic complete response; Q3W = every 3 weeks; TTDM = time to death or distant metastases.

^a The March 2023 submission noted (p86) that a claim is not being made based on the use of pCR or MPR as surrogates for OS, as follow-up for OS in the CM816 trial is ongoing. Pathological endpoints were only presented as they are co-primary and secondary endpoints in the CM816 trial.

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Requested listing

3.1 The resubmission proposed a listing that excluded patients with non-squamous type NSCLC and known sensitising epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) alterations. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
MEDICINAL PRODUCT Form	PBS item code	Maximum amount	No. of Repeats
NIVOLUMAB Injection	New (Public) New (Private) MP	360 mg	2
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			
Authority Required (STREAMLINED)			
Indication: Non-small cell lung cancer Resectable (tumours \geq 4 cm or node positive) non-small cell lung cancer (NSCLC)			

Clinical criteria:
<i>The condition must be at least one of: (i) node positive, (ii) at least 4 cm in size</i>
AND
Clinical criteria:
<i>The treatment must be for the purpose of neoadjuvant use to the primary treatment of surgical resection, as a once per lifetime course of 3 doses</i>
<i>Patient must be preparing for surgical resection (neoadjuvant treatment)</i>
AND
Clinical criteria:
<i>Patient must have a WHO performance status of 0 or 1</i>
AND
Clinical criteria:
<i>For patients with non-squamous type non-small cell lung cancer, the condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material</i>
AND
Clinical criteria:
<i>The treatment must be in combination with platinum-based chemotherapy</i>
AND
Clinical criteria:
<i>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC; or</i>
<i>The condition must be squamous type non-small cell lung cancer</i>
AND
Clinical criteria:
<i>The treatment must not exceed a total of 3 doses of nivolumab</i>
<i>The condition must have had, where treatment is for non-squamous type disease, both the following excluded through tumour material sampling: (i) epidermal growth factor receptor (EGFR) gene rearrangement, (ii) anaplastic lymphoma kinase (ALK) gene rearrangement.</i>
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

- 3.2 The resubmission proposed a special pricing arrangement (SPA) with an effective public hospital dispensed price for maximum amount (DPMA) of \$ | (published \$7,189.55) and an effective private hospital DPMA of \$| (published \$7,330.61). The effective ex-manufacturer price (EMP) in the resubmission of \$| per 100 mg vial is 34.2% lower than the \$| per 100 mg vial proposed in the March 2023 submission.
- 3.3 In March 2023, the PBAC noted the short duration of neoadjuvant nivolumab therapy and advised that use of subsequent immunotherapy in those who relapse with metastatic disease may be clinically appropriate, but expressed a preference for supportive evidence to support such use (paragraph 7.5, nivolumab Public Summary Document (PSD), March 2023 PBAC meeting). The resubmission noted that current PBS restrictions for nivolumab, pembrolizumab, cemiplimab, and atezolizumab for the treatment of metastatic NSCLC disease specify that the patient must not have received prior treatment with a programmed cell death ligand-1 (PD-L1) inhibitor for NSCLC. The resubmission proposed the following change (**bolded**) to the current clinical criteria: Patient must not have received prior treatment with a PD-1 inhibitor or a PD-L1 inhibitor for **treatment of Stage IV (metastatic)** non-small cell lung cancer. No new

evidence to support use of subsequent immunotherapy was provided in the resubmission.

- 3.4 Flow on effects to the Medicare Benefits Schedule (MBS): Nil. In November 2022 the Medical Services Advisory Committee (MSAC) recommended the creation of new MBS items for small next generation sequencing panels for biomarker testing of patients with NSCLC which includes testing of EGFR and ALK status for access to therapies listed on the PBS (Application No. 1721 Small gene panel testing for NSCLC PSD, November 2022 MSAC meeting).

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The comments from Lung Foundation Australia highlight the significant burden of lung cancer on people living with the condition, their families and the Australian health system. The comments also highlight the need for additional treatment options for lung cancer that allow patients to live a better and healthier life with their condition.
- 4.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the nivolumab submission, categorising it as one of the therapies of 'highest priority for PBS listing' on the basis of the Checkmate 816 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nivolumab, which was a Grade A. This is the highest grade on a scale from A to C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies¹.

Comparative effectiveness

- 4.4 The primary evidence of the March 2023 submission and the current resubmission was based on a direct randomised open-label trial (CM816) comparing nivolumab (360 mg intravenous [IV] Q3W for a maximum of 3 cycles) plus platinum-doublet chemotherapy (neoNIVO+neoChemo) with platinum-doublet chemotherapy (neoChemo), as neoadjuvant treatment for resectable early stage NSCLC (Stage IB

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

(≥ 4 cm) – IIIA, American Joint Commission on Cancer (AJCC), 7th Edition). In March 2023, effectiveness data from the CM816 trial were based on two data cutoff dates:

- Final analysis of co-primary endpoint of pathological complete response (pCR) rate: data cutoff 16 September 2020; and
- Interim analysis 1 of event free survival (EFS) and overall survival (OS): data cutoff 20 October 2021 (paragraph 6.10, nivolumab PSD, March 2023 PBAC meeting).

4.5 In March 2023, the PBAC considered that the claim of superior comparative effectiveness compared to neoChemo was reasonable (paragraph 7.8, nivolumab PSD, March 2023 PBAC meeting). The PBAC considered the claim of non-inferior comparative safety compared with neoChemo was not adequately supported by the data due to an increased risk of immune checkpoint-related adverse events (AEs) (paragraph 7.10, nivolumab PSD, March 2023 PBAC meeting).

4.6 The resubmission provided data from Interim analysis 2 of EFS, time to death or distant metastasis (TTDM), OS and safety in an Appendix. The resubmission stated the updated analysis of the CM816 trial corroborates the outcomes presented in the submission considered by the PBAC in March 2023.

4.7 The EFS results for Interim analysis 1 and Interim analysis 2 are summarised in Table 3. The EFS Kaplan-Meier (KM) curves reported at Interim analysis 2 are presented in Figure 1. It was stated in the resubmission that due to less censoring at Interim analysis 2, median EFS was not reached.

Table 3: Duration of event-free survival in CheckMate 816: Interim analysis 1 and Interim analysis 2

	NIVO+chemo		Chemo		Difference in median	Hazard ratio (95% CI)
	n/N with event (%)	Median time-to-event (95% CI)	n/N with event	Median time-to-event (95% CI)		
Interim analysis 1: median follow-up 29.5 months						
Randomised/ITT	64/179 (36%)	31.6 (30.2, NR)	87/179 (49%)	20.8 (14.0, 26.7)	10.8	0.63 (0.45, 0.87)
Interim analysis 2: median follow-up 41.4 months						
Randomised/ITT	-/179 ^a	NR (31.6, NR)	-/179 ^a	21.1 (14.8, 42.1)	-	0.68 (0.49, 0.93)

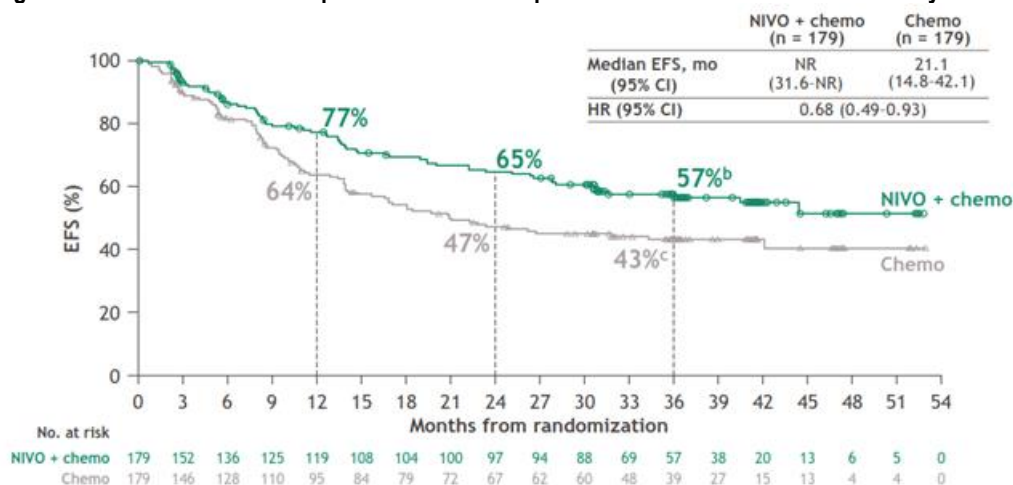
Source: Table 10, p16 of the resubmission

Chemo = chemotherapy; CI = confidence interval; ITT = intention to treat; NR = not reached; NIVO = nivolumab

Blue shading represents information previously considered by the PBAC.

^a Data not provided in resubmission.

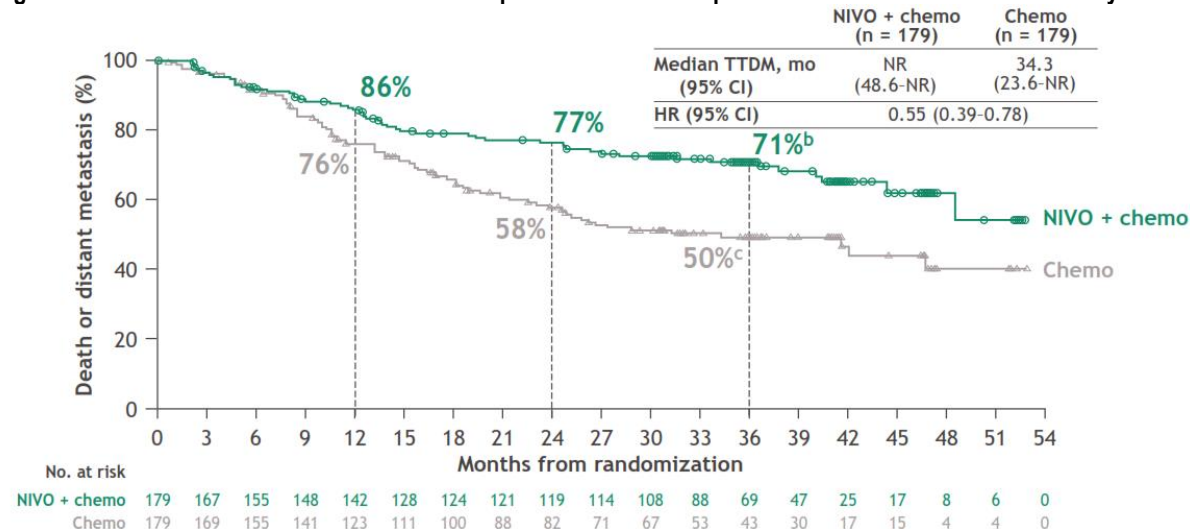
Figure 1: Event free survival Kaplan-Meier curves reported in CheckMate 816: Interim analysis 2



Source: Figure 1, p17 of the resubmission

4.8 The TTDM KM curves reported at Interim analysis 2 are presented in Figure 2. For comparison, the hazard ratio (HR) reported for TTDM at Interim analysis 1 was 0.53 (95% CI 0.36, 0.77). The Interim analysis 2 data for this outcome was used in the financial estimates (see paragraph 4.25).

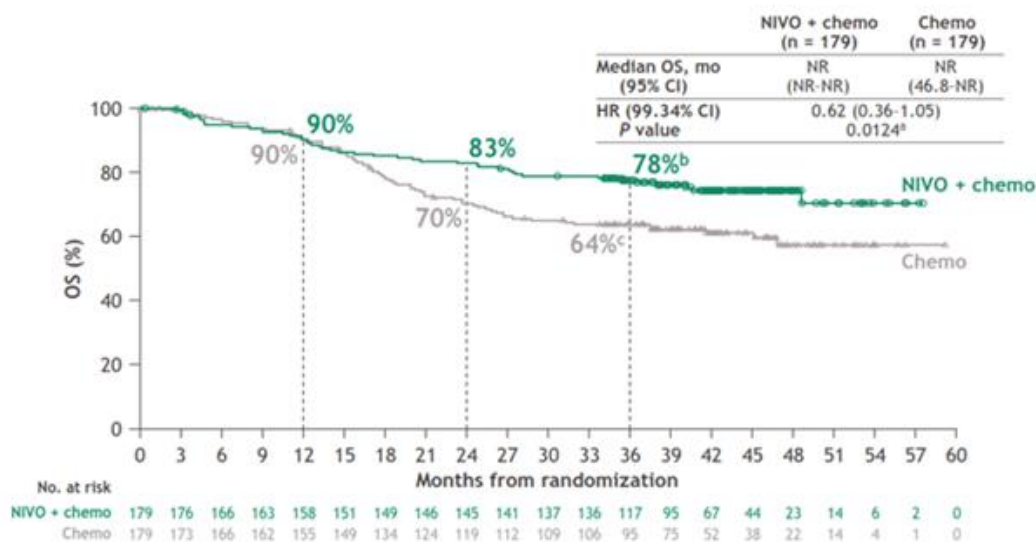
Figure 2: Time to death or distant metastases Kaplan-Meier curves reported in CheckMate 816: Interim analysis 2



Source: Figure 2, p18 of the resubmission

4.9 The OS KM curves reported at Interim analysis 2 are presented in Figure 3. For comparison, the HR reported for OS at Interim analysis 1 was HR = 0.57 (99.67% CI 0.30, 1.07; P=0.008).

Figure 3: Overall survival Kaplan-Meier curves reported in CheckMate 816: Interim analysis 2



Source: Figure 3, p19 of the resubmission

Clinical claim

- 4.10 The PBAC reiterated its March 2023 advice that the claim of superior comparative effectiveness compared to neoChemo was reasonable (see paragraph 4.5).
- 4.11 The PBAC reiterated its March 2023 advice that the claim of non-inferior comparative safety compared with neoChemo was not adequately supported by the data (see paragraph 4.5).

Economic analysis

- 4.12 In March 2023, the submission presented a cost-utility analysis with a 25 year time horizon and a resulting base case incremental cost-effectiveness ratio (ICER) of \$25,000 to < \$35,000 per quality-adjusted life years (QALY) gained. Overall, the PBAC considered the model results to be highly uncertain and likely optimistic. The PBAC noted that the incremental life years (LYs) and QALYs gained with the addition of nivolumab over the trial period were small (0.09 LY and 0.10 QALY) but increased substantially over the 25 year model time horizon to 1.23 LY and 1.03 QALYs (discounted estimates; 2.12 LYs and 1.74 QALYs with discounting removed). The PBAC further noted structural uncertainty with the model due to the assumption of an ongoing treatment effect, assumptions regarding cure time points and modelling the distant metastasis (DM) health state as an absorbing state in which cost-ineffective therapies were applied (paragraph 7.13, nivolumab PSD, March 2023 PBAC meeting).
- 4.13 In March 2023, the PBAC noted that when using a time horizon of 15 years, an onset of cure of 6 years in the neoNIVO+neoChemo arm and the EFS and locoregional recurrence (LR) health state utilities from Grutters et al 2010, the ICER increased from \$25,000 to < \$35,000 per QALY gained to \$45,000 to < \$55,000 per QALY gained. The PBAC noted for this scenario the estimated QALY gain was 0.61 (discounted), which

although less than the submission's base case estimate of 1.03, remained highly uncertain given the extent of extrapolation and issues noted with the model structure. The PBAC considered that an ICER of not more than \$30,000 per QALY gained would be appropriate in this context and noted that a price reduction would be required for nivolumab to be considered cost-effective (paragraph 7.18, nivolumab PSD, March 2023 PBAC meeting).

- 4.14 In March 2023, the PBAC considered that the outstanding issues associated with the economic model may be addressed with the use of a re-specified base case that includes a time horizon of 15 years, an onset of cure of 6 years in the neoNIVO+neoChemo arm and the EFS and LR health state utilities from Grutters et al 2010 and that incorporates a price reduction that results in an ICER of not more than \$30,000 per QALY gained (paragraph 7.21, nivolumab PSD, March 2023 PBAC meeting).
- 4.15 The resubmission provided an updated economic model with a base case ICER of \$25,000 to < \$35,000 per QALY gained. The updated model included the following amendments:
- Reduced the effective EMP to \$| per 100 mg vial from \$| per 100 mg vial.
 - Reduced the time horizon to 15 years from 25 years. The use of a 15 year time horizon was consistent with the March 2023 PBAC recommendations (see paragraph 4.14).
 - Applied EFS and LR health state utilities from Grutters et al 2010 (EFS = 0.760 and LR = 0.740). The use of EFS and LR health state utilities from Grutters et al 2010 was consistent with the March 2023 PBAC recommendations (see paragraph 4.14).
 - Delayed the onset of cure to 6 years in both treatment arms from 5 years. In March 2023 the PBAC advised that it would be more appropriate for the onset of cure to be delayed from 5 years to 6 years in the neoNIVO+neoCHEMO arm of the economic model (paragraph 7.15, nivolumab PSD, March 2023 PBAC meeting). The resubmission argued that regardless of the timepoint selected (5 years or 6 years for the onset of cure), the same timepoint should be applied for the intervention and treatment arm. The resubmission reiterated that where onset of cure has been applied at different timepoints previously it has been related to the duration of treatments. The resubmission provided the example of the osimertinib NICE TA761 submission, where the External Assessment Group (EAG) applied differential cure timepoints (8 years in intervention arm and 5 years in best supportive care arm) to account for treatment time with osimertinib (i.e., 5 years plus the 3-year maximum adjuvant osimertinib treatment time). The resubmission argued that as neoNIVO is used concomitantly with neoChemo and that the treatment duration is 3 cycles only, incorporating the delay of time point for cure for neoNIVO+neoChemo is biased against nivolumab. Amending the onset of cure to 6 years in both treatment arms was not consistent with the

March 2023 PBAC recommendations (see paragraph 4.14). An onset of cure of 6 years in the neoNIVO+neoCHEMO arm and of 5 years in the neoCHEMO arm results in an ICER of \$25,000 to < \$35,000 per QALY gained. An effective EMP of \$ per 100 mg vial would be required to achieve an ICER of \$30,000 per QALY gained in this scenario. The pre-PBAC response reiterated that it was appropriate for the onset of cure to be the same for both neoNIVO+neoCHEMO and neoCHEMO as both treatment regimens occur at the same time and for the same duration.

Estimated PBS usage & financial implications

- 4.16 In March 2023, the PBAC noted the approach taken to estimate the use of nivolumab and agreed with the ESC that the assumed uptake rate was likely to be reasonable. The PBAC previously noted MSAC support for the creation of a national lung cancer screening program and that this may make it likely that more patients would be identified who were suitable for neoadjuvant treatment, although the timing and impact were unknown at the time. The PBAC previously noted the only cost-offsets considered in the financial estimates related to the use of chemotherapy. The PBAC previously considered cost-offsets associated with reduced use of adjuvant atezolizumab, durvalumab in borderline resectable stage III NSCLC and immunotherapy for metastatic disease should be accounted for in any revised estimates; and anticipated as a result that there would be only a small increase in expenditure for immunotherapies for NSCLC (paragraph 7.19, nivolumab PSD, March 2023 PBAC meeting).
- 4.17 The resubmission provided revised financial estimates that included the following amendments:
- Applied an effective EMP of \$ per 100 mg vial and \$ per 40 mg vial.
 - Incorporated additional patients from adjuvant atezolizumab in Stage II-III A and durvalumab in borderline resectable Stage III;
 - Incorporated cost-offsets from reduced use of adjuvant atezolizumab in Stage II-III A, PD-L1 >50% NSCLC;
 - Incorporated cost-offsets from reduced use of durvalumab in borderline resectable Stage III NSCLC; and
 - Incorporated cost-offsets from the reduced use of immunotherapy in the metastatic setting for patients achieving a cure with neoadjuvant treatment. Pembrolizumab was applied as a proxy for all metastatic PD-(L)1 treatment options. The resubmission stated that pembrolizumab currently holds the majority of the market share for NSCLC (60.7%; refer to Table 9, p28 of the Public

Release Document for the September 2022 DUSC review of NSCLC listings²), with other treatments being cost-minimised to pembrolizumab.

- 4.18 Consistent with the March 2023 submission the financial estimates included eligible patients with Stage IB, II and IIIA non-squamous and squamous type NSCLC.
- 4.19 In order to calculate the impact associated with the reduced use of immunotherapies within the adjuvant and metastatic setting, the resubmission sought advice from 6 Australian oncologists that were stated by the resubmission to specialise in the treatment of NSCLC. The revised estimates only consider the use of the immunotherapy (nivolumab, atezolizumab, durvalumab or pembrolizumab) component of treatment and not any chemotherapy agents used prior to, or in combination with immunotherapies. The resubmission stated that the inclusion of chemotherapy costs would not have a material impact on the results. Based on the average of the responses provided by the 6 oncologists (p10 of the resubmission), the submission assumed that 46% of patients currently considered for treatment with adjuvant chemotherapy followed by atezolizumab would be treated with neoNIVO+neoChemo. The estimated proportion of patients currently treated with durvalumab that would be treated with neoNIVO+neoChemo was assumed to be 11%. It was also estimated that 84% of patients treated with neoNIVO+neoChemo would be retreated with an immunotherapy upon progression/recurrence to metastatic disease.
- 4.20 The resubmission assumed that the patients who would be treated with neoNIVO+neoChemo instead of atezolizumab or durvalumab were not captured in the estimates of use included in the March 2023 submission, and hence added these patients to the total pool of patients (Table 4). The pre-PBAC response stated that the financial estimates in the March 2023 submission did not account for the substitution of atezolizumab and durvalumab for neoNIVO+neoChemo and therefore incorporating cost offsets for the expected reduced use of atezolizumab and durvalumab resulted in an increase in the number of patients treated with neoNIVO+neoChemo compared with the March 2023 estimates.
- 4.21 The number of patients treated with neoNIVO+neoChemo instead of atezolizumab or durvalumab was estimated using an epidemiological approach rather than a market share approach. The pre-PBAC response argued that an epidemiological approach was appropriate as the value of adopting a market share approach would be limited by the immaturity of the adjuvant atezolizumab market and the lack of exchangeability between the PBS populations for PBS-listed durvalumab and the proposed PBS-listing for neoNIVO+neoChemo.

² <https://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2022-09/durvalumab-NSCLC-24-month-review-DUSC-PRD-2022-09.docx>

- 4.22 For atezolizumab the total number of patients was calculated as resectable Stage II-III NSCLC (non-squamous without ALK or EGFR, squamous) with an ECOG PS 0-1 and PD-L1 >50%, and of this 33.21% (NIVO uptake of 72.46% x replacement of 46%) of patients are assumed to be treated with neoNIVO+neoChemo. The PBAC noted that in undertaking this calculation the resubmission had incorrectly multiplied the proportion of non-squamous without ALK or EGFR patients by the proportion of squamous NSCLC patients rather than adding these two patient groups. Correcting this increased the number of patients estimated to be treated with neoNIVO+neoChemo instead of atezolizumab (increased from < 500 to < 500 patients in Year 1, and increased from < 500 to < 500 patients in Year 6).
- 4.23 For durvalumab the total number of patients was calculated as unresectable Stage III NSCLC with an ECOG PS 0-1, and of this 7.85% (NIVO uptake of 72.46% x replacement of 11%) of patients are assumed to be treated with neoNIVO+neoChemo. The PBAC noted that in Year 1 only, the proportion considered unresectable applied was 15.6% instead of 20%. Correcting this resulted in an increase in the number of patients estimated to be treated with neoNIVO+neoChemo instead of durvalumab in Year 1 (increased from < 500 to < 500 patients).
- 4.24 The PBAC noted that based on a comparison with financial estimates previously considered by the PBAC it appeared that the corrected number of atezolizumab patients (paragraph 4.22) were likely to be overestimated and the corrected number of durvalumab patients (paragraph 4.23) remained underestimated, however considered that the total cost offset estimated for both atezolizumab and durvalumab was likely reasonable.
- 4.25 The resubmission also assumed that there would be a 21% reduction in distant metastases and subsequent metastatic immunotherapy costs associated with the treatment of neoNIVO. This assumption was based on data from the assessment of TTDM reported from the 3-year update of the CM816 (see paragraph 4.8). Hence, the number of patients treated with neoNIVO+neoChemo in each year was multiplied by 0.21 and then multiplied by 0.84 (those that would have been treated with immunotherapy in the metastatic setting; see paragraph 4.19) to estimate the number of patients who would not require subsequent metastatic immunotherapy as a result of neoNIVO (Year 1 = < 500 patients increasing to Year 6 = <500 patients). These figures were used to estimate the reduction in cost to the PBS/RPBS for pembrolizumab. The PBAC noted that correcting the errors in the resubmission financial estimates identified in paragraphs 4.22 and 4.23 increased the number of patients treated with neoNIVO+neoChemo and hence would reduce the number of patients who would require subsequent metastatic immunotherapy as a result of neoNIVO (Year 1 = < 500 patients increasing to Year 6 = <500).
- 4.26 The resubmission estimated a net cost to the PBS/RPBS of \$10 million to < \$20 million in Year 6 of listing, with a total net cost to the PBS/RPBS of \$80 million to < \$90 million over the first 6 years of listing (Table 4). The resubmission noted that the net cost was calculated based on the published price of atezolizumab and durvalumab and the

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effective price of pembrolizumab. The resubmission stated that with the application of all effective prices of these treatments, the net cost is expected to be greater than the estimate presented in Table 4. The PBAC considered that the financial estimates would need to be corrected for the errors identified in paragraphs 4.22 to 4.23 and updated with effective prices.

Table 4: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Stage 1b NSQ	1	1	1	1	1	1
Stage II NSQ	1	1	1	1	1	1
Stage IIIa NSQ	1	1	1	1	1	1
Stage 1b SQ	1	1	1	1	1	1
Stage II SQ	1	1	1	1	1	1
Stage IIIa SQ	1	1	1	1	1	1
Adjuvant atezolizumab	1	1	1	1	1	1
Unresectable durvalumab	1	1	1	1	1	1
Total number of patients treated^a	2	2	2	2	2	2
Number of scripts dispensed	2	2	2	2	2	2
Estimated extent of use March 2023 submission						
Number of patients treated	2	2	2	2	2	2
Number of scripts dispensed	2	2	2	2	2	2
Estimated financial implications of nivolumab						
Total cost to the PBS/RPBS, including patient copayments(\$)	3	3	3	3	3	3
Estimated financial implications of nivolumab March 2023 submission						
Total cost to the PBS/RPBS, including patient copayments(\$)	4	4	4	4	4	4
Estimated financial implications for reduced use of immunotherapies in other settings						
Atezolizumab^b						
- Number of patients	- 1	- 1	- 1	- 1	- 1	- 1
- Number of scripts	- 1	- 1	- 1	- 1	- 1	- 1
- Net cost	5	5	5	5	5	5
Durvalumab^c						
- Number of patients	- 1	- 1	- 1	- 1	- 1	- 1
- Number of scripts	- 1	- 1	- 1	- 1	- 2	- 2
- Net cost	5	5	5	5	5	5
Pembrolizumab^d						
- Number of patients	- 1	- 1	- 1	- 1	- 1	- 1
- Number of scripts	- 2	- 2	- 2	- 2	- 2	- 2
- Net cost (\$)	5	5	5	5	5	5
Total cost to the PBS/RPBS, including patient copayments (\$)	5	5	5	5	5	5
Estimated financial implications for other medicines March 2023 submission						
Cost to the PBS/RPBS, including patient copayments ^e (\$)	5	5	5	5	5	5
Net financial implications						
Net cost to PBS/RPBS(\$)	6	6	6	6	6	6
Net cost to MBS(\$)	7	7	7	7	7	7
Net cost to PBS/RPBS/MBS(\$)	6	6	6	6	6	6

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net financial implications March 2023 submission						
Net cost to PBS/RPBS(\$)	4	4	4	4	4	4
Net cost to MBS(\$)	5	5	5	5	5	5
Net cost to PBS/RPBS/MBS(\$)	4	4	4	4	4	4

Source: Compiled during the preparation of the submission overview, based on Table 6, Table 7, p11, Table 8, pp12-13 and Table 9 p14 of the resubmission and Excel workbook 'Attachment 2 - Nivolumab Neoadjuvant NSCLC Utilisation and Cost Model_early reentry resubmission'.

NSQ = non-squamous; SQ = squamous

^a Compared to March 2023 submission this includes additional patients for: adjuvant Stage II-IIIa, PD-L1 >50% atezolizumab Year 1 < 500, Year 2 < 500, Year 3 < 500, Year 4 < 500, Year 5 < 500, Year 6 < 500); unresectable stage III use of durvalumab Year 1 < 500, Year 2 < 500, Year 3 < 500, Year 4 < 500, Year 5 < 500, Year 6 < 500)

^b Adjuvant Stage II-IIIa, PD-L1 >50% NSCLC

^c Unresectable Stage III NSCLC

^d Pembrolizumab as a proxy for all metastatic PD-(L)1 treatment options.

^e Estimated changes in costs of chemotherapies in neoadjuvant and adjuvant settings

Blue shading represents information previously considered by the PBAC.

The redacted values correspond to the following ranges:

¹ <500

² 500 to < 5,000

³ \$20 million to < \$30 million

⁴ \$30 million to < \$40 million

⁵ net cost saving

⁶ \$10 million to < \$20 million

⁷ \$0 to < \$10 million

Financial Management – Risk Sharing Arrangements

4.27 In March 2023, the PBAC considered that it would be appropriate for nivolumab for the proposed population to be included in the current risk sharing arrangement (RSA) in place for immunotherapies for NSCLC given the overlapping patient populations and expected reduced use of immunotherapy in metastatic disease due to a proportion of patients being cured in the adjuvant setting. The PBAC considered it would likely be appropriate for the financial caps to be increased, however expected the increase to be small once the reduced use of immunotherapy in the adjuvant and metastatic settings are accounted for. The PBAC further considered it would be appropriate to manage the uncertainties associated with retreatment with immunotherapy in metastatic disease within the RSA, given there is no clinical data to support such use (paragraph 7.20, nivolumab PSD, March 2023 PBAC meeting).

4.28 The resubmission stated that the sponsor is willing to negotiate increased financial caps and enter into a RSA in order to provide greater certainty of forecast expenditure for this indication. However, the resubmission proposed that the requirement for an RSA and negotiated increase in financial caps be re-assessed in consideration of the overall net cost to the PBS/RPBS calculated using the effective price for neoNIVO and effective prices for adjuvant atezolizumab, durvalumab and metastatic pembrolizumab.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended listing nivolumab in combination with chemotherapy as neoadjuvant treatment of resectable non-small cell lung cancer (NSCLC). The PBAC was satisfied that neoadjuvant nivolumab plus neoadjuvant chemotherapy (neoNIVO+neoChemo) provides, for some patients, a significant improvement in efficacy over neoadjuvant chemotherapy (neoChemo). The PBAC considered that the amendments made in the resubmission, including the exclusion of patients with known sensitising epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) alterations, changes to the economic evaluation and a reduced price had sufficiently addressed the Committee's previous concerns. However, the PBAC considered the utilisation of nivolumab was overestimated and the cost-offsets associated with the current use of immunotherapy in the financial estimates remained underestimated, in part due to not accounting for repeat use of immunotherapy in the metastatic setting being precluded.
- 5.2 The PBAC noted the input from Lung Foundation Australia that highlighted the need for additional treatment options for this condition. In addition, the PBAC noted the Medical Oncology Group of Australia's strong support for the submission. Noting the availability of moderately effective peri-operative therapies and multiple therapies for metastatic disease, and that OS for patients with NSCLC is currently approximately 45% at 5 years, the PBAC reiterated its March 2023 advice that there remains an unmet clinical need for more effective therapies for resectable lung cancer (paragraph 7.2, nivolumab PSD, March 2023 PBAC meeting).
- 5.3 With regard to the requested PBS restriction, the PBAC advised that:
- Subsequent use of immunotherapy in those who relapse with metastatic disease could not be supported by the Committee at this time. In March 2023, the PBAC had considered use in this way may be clinically appropriate, but expressed a preference for evidence to support such use (paragraph 7.5, nivolumab PSD, March 2023 PBAC meeting). The PBAC noted that the resubmission did not provide evidence to support use of subsequent immunotherapy. The PBAC acknowledged that it would reconsider this recommendation to exclude retreatment in metastatic disease should evidence supporting such use become available. For this reason, the PBAC considered that a treatment criterion stating that a 'Patient must not be undergoing treatment with more than 3 PBS-subsidised doses of this drug per lifetime for this indication' would be appropriate to include in the restriction.
 - In non-squamous type NSCLC where an activating EGFR gene mutation or ALK gene rearrangement is detected, nivolumab must not be a PBS-benefit. Phrasing of this eligibility requirement would be appropriate as a 'Prescriber Instruction' as opposed to a 'Clinical criteria' given that EGFR/ALK gene abnormality investigations may not be possible for each patient.

- The clinical criteria stating that ‘The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC; or The condition must be squamous type non-small cell lung cancer’ can be replaced with the PBS indication of: ‘non-small cell lung cancer’.
- 5.4 The PBAC reaffirmed its March 2023 advice that neoChemo as the nominated main comparator was appropriate (paragraph 7.6, nivolumab PSD, March 2023 PBAC meeting).
- 5.5 The resubmission was based on a direct randomised open-label trial (CM816) comparing neoNIVO+neoChemo with neoChemo, as neoadjuvant treatment for resectable early stage NSCLC. The resubmission provided data from Interim analysis 2 of event free survival (EFS), time to death or distant metastasis (TTDM), overall survival (OS) and safety. The PBAC noted that at a median follow up of 41.4 months neoNIVO+neoChemo was associated with a statistically significant improvement in EFS compared with neoChemo (HR = 0.68; 95% confidence interval [CI]: 0.49, 0.93), comparable to that reported in March 2023 (HR = 0.63; 95% CI: 0.45, 0.87). Acknowledging the updated interim OS data remained immature, the PBAC noted the results continued to indicate a trend to improved survival favouring neoNIVO+neoChemo over neoChemo (HR for death = 0.62; 99.34% CI: 0.36, 1.05). The PBAC reaffirmed its March 2023 advice that the claim of superior comparative effectiveness for neoNIVO+neoChemo versus neoChemo was supported by the data presented for EFS which indicated a moderate benefit for this outcome (paragraph 7.8, nivolumab PSD, March 2023 PBAC meeting).
- 5.6 The PBAC reaffirmed its March 2023 advice that the claim of non-inferior safety was not supported by the clinical evidence provided in the submission (paragraph 7.10, nivolumab PSD, March 2023 PBAC meeting).
- 5.7 The PBAC noted that the resubmission provided an economic model with a re-specified base case that incorporated a 15 year time horizon, EFS and LR health state utilities from Grutters et al 2010 and a price reduction that resulted in an ICER of \$25,000 to < \$35,000 per QALY gained, in line with previous PBAC advice (paragraph 7.21, nivolumab PSD, March 2023 PBAC meeting). However, the re-specified base case did not incorporate an onset of cure of 6 years in the neoNIVO+neoChemo arm and 5 years in the neoChemo arm, with the pre-PBAC response continuing to argue that it was appropriate for the onset of cure to be the same for both neoNIVO+neoCHEMO and neoCHEMO. The PBAC considered the data from Interim analysis 2 of the CM816 trial increased certainty in the trial effects and the resulting modelled benefits. The PBAC therefore advised that the re-specified base case and price proposed in the resubmission addressed previous concerns regarding the cost-effectiveness of nivolumab. The PBAC noted however, that if data becomes available that supports the use of immunotherapy in both the neoadjuvant and adjuvant settings that the cost-effectiveness of use solely in the neoadjuvant setting may need to be reassessed.

- 5.8 The PBAC noted that the resubmission had provided revised financial estimates that incorporated cost-offsets for adjuvant atezolizumab, durvalumab and reduced immunotherapy in the metastatic setting due to a cure being achieved with neoadjuvant therapy but considered they remained underestimated due to calculation errors (see paragraphs 4.22 to 4.25). The PBAC also considered that it remained unclear why atezolizumab patients would not have been captured in the incident population for Stages II-III A and durvalumab in the Stage III patient estimates from the March 2023 submission. For this reason, the PBAC advised that it was likely not appropriate to include additional patients in the total pool of patients.
- 5.9 The PBAC noted that cost-offsets to account for repeated use of immunotherapy for metastatic disease being precluded were not incorporated. The PBAC considered that this may be achieved by using the approach in the resubmission for estimating offsets in the metastatic setting due to treatment cures, but with the offset increasing from 21% to 50% based on 29% (100% - 71%) of patients who receive neoNIVO+neoCHEMO going on to develop metastatic disease (see 36 month TTDM data, Figure 2) and not receiving repeat immunotherapy. The sponsor may wish to provide alternate data that excludes 'death in the absence of distant metastasis' from this estimate.
- 5.10 The PBAC recalled that it had previously considered the assumed uptake of nivolumab was likely reasonable and noted MSAC support for the creation of a national lung cancer screening program which may lead to more patients being identified who would be suitable for neoadjuvant treatment (paragraph 7.19, nivolumab PSD, March 2023 PBAC meeting). However, the PBAC noted that treatment with neoadjuvant nivolumab would require a change to current clinical practice with surgery being delayed until the completion of treatment and therefore considered the uptake of nivolumab in the first 2 years of listing uncertain. The PBAC considered the uptake of nivolumab may be lower than estimated (72.5% for eligible Stage IB, II and III A patients) and advised that an uptake of 30-40% per annum in the first 2 years of listing may be a more reasonable estimate of uptake.
- 5.11 The PBAC advised that the financial estimates would be acceptable once corrected for the errors identified in paragraphs 4.22 to 4.23, the additional atezolizumab and durvalumab patients were removed, the cost-offsets were updated to assume no repeat use of immunotherapy for metastatic disease, a 30-40% uptake of nivolumab in the first two years of listing and effective prices were incorporated.
- 5.12 The PBAC reaffirmed its March 2023 advice, that it would be appropriate for nivolumab for the proposed population to be included in the current RSA for immunotherapies for NSCLC given the overlapping patient populations and expected reduced use of immunotherapy in metastatic disease due to a proportion of patients being cured in the adjuvant setting (paragraph 7.20, nivolumab PSD, March 2023 PBAC meeting). The PBAC considered an increase in the financial caps consistent with the financial estimates accepted by the Committee in paragraph 5.11 would be appropriate.

5.13 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for nivolumab:

- a) The treatment is expected to provide a moderate improvement in EFS over neoChemo on the basis of the clinical evidence from the CM816 trial and hence the criteria of providing a substantial and clinically relevant improvement in efficacy was not met;
- b) Acknowledging an unmet clinical need remains, the treatment is not expected to address a high and urgent unmet clinical need due to the availability of alternative therapies (see paragraph 5.2);
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

5.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Add new indication as follows:

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
MEDICINAL PRODUCT Form	PBS item code	Maximum amount	No. of Repeats
NIVOLUMAB Injection	New (Public) New (Private) MP	360 mg	2
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			
Restriction Summary / Treatment of Concept: [New 1] : Authority Required (STREAMLINED)			
New IND1	Indication: Resectable non-small cell lung cancer (NSCLC)		
New CC1	Clinical criteria:		
New CC1.1	The condition must be at least one of: (i) node positive, (ii) at least 4 cm in size		
	AND		
New CC2	Clinical criteria:		
New CC2.1	The treatment must be for neoadjuvant use in a patient preparing for surgical resection		
	AND		
10859	Clinical criteria:		

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10858	Patient must have a WHO performance status of 0 or 1
	AND
21343	Clinical criteria:
21344	The treatment must be in combination with platinum-based chemotherapy
New TC1	Treatment criteria:
New TC1.1	Patient must not be undergoing treatment with more than 3 PBS-subsidised doses of this drug per lifetime for this indication
New PI1	Prescribing Instructions: In non-squamous type NSCLC where any of the following is known to be present, this drug must not be a PBS-benefit: (i) activating epidermal growth factor receptor (EGFR) gene mutation, (ii) anaplastic lymphoma kinase (ALK) gene rearrangement.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

The Sponsor welcomes the PBAC's recommendation of nivolumab for the neoadjuvant treatment of NSCLC but is disappointed that the PBAC did not support the retreatment with immunotherapy for patients who recur in the metastatic NSCLC setting.