

## **6.07 NIVOLUMAB,**

**Injection concentrate for I.V. infusion 40 mg in 4 mL,  
Injection concentrate for I.V. infusion 100 mg in  
10 mL, Opdivo<sup>®</sup>,  
Bristol Myers Squibb Australia Pty Ltd**

### **1 Purpose of submission**

- 1.1 The Category 2 submission requested modification of the proposed listing for nivolumab for the neoadjuvant treatment of surgically-resectable non-small cell lung cancer (NSCLC), following the recommendations of the PBAC for this indication in July 2023.
- 1.2 The restriction recommended in July 2023 allowed three doses of nivolumab in a patient's lifetime, so that immunotherapy (IO) retreatment with nivolumab or another programmed death-ligand 1 (PD-L1) inhibitor of patients relapsing after neoadjuvant treatment was precluded.
- 1.3 The sponsor proposed two alternative modifications to the recommended listing, referred to as Option A and Option B. Option A, the sponsor's preferred option, proposed modifying the recommended restriction to allow IO retreatment. Option B proposed not allowing IO retreatment, but increasing the ex-manufacturer price from \$| per 100 mg to \$| per 100 mg.
- 1.4 Listing was requested on the basis of a cost-effectiveness analysis versus platinum-based neoadjuvant chemotherapy (neoChemo), as previously considered appropriate by the PBAC (para 7.6, nivolumab public summary document [PSD], March 2023 PBAC meeting).
- 1.5 The PICO from the previous submissions is presented in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients with resectable (tumours $\geq$ 4cm or node positive) NSCLC
Intervention	Nivolumab, 360 mg Q3W plus chemotherapy Q3W
Comparator	Main: Neoadjuvant chemotherapy Additional: • Adjuvant chemotherapy • Adjuvant chemotherapy followed by atezolizumab
Outcomes	Primary: EFS Key secondary: OS, TTDM, HRQoL, pCR, MPR, safety
Clinical claim	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 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.

## 2 Background

### **Registration status**

- 2.1 The TGA approved indications for nivolumab include NSCLC as well as several other types of cancer.<sup>1</sup>
- 2.2 Nivolumab is PBS-listed for the second-line treatment of locally advanced or metastatic NSCLC, and in combination with ipilimumab for the first-line treatment of metastatic NSCLC of squamous histology, however patients who have received prior treatment for NSCLC with a PD-L1 inhibitor (nivolumab, pembrolizumab or atezolizumab) are excluded.

### **Previous PBAC consideration**

- 2.3 This is the third consideration of nivolumab in combination with chemotherapy for the neoadjuvant treatment of patients with resectable NSCLC. The PBAC previously considered neoadjuvant nivolumab (neoNIVO) for resectable NSCLC in March 2023 and July 2023. A summary of matters of concern and how they were addressed in the current submission is presented in Table 2.
- 2.4 In March 2023, the PBAC noted that IO retreatment was assumed by the submission, and included in the economic models, which would require modification of the PBS-listings for PD-L1 inhibitors. The PBAC noted that although there was a 'clinical

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<sup>1</sup> <https://www.tga.gov.au/sites/default/files/2023-06/auspar-opdivo-230606-pi.pdf>, accessed 13 November, 2023.

- rationale' for IO retreatment, and that it was 'clinically appropriate', 'there is currently insufficient evidence to support retreatment with PD-L1 inhibitors in metastatic disease' (paras 3.11, 7.17, nivolumab PSD, March 2023 PBAC meeting).
- 2.5 The PBAC previously stated that if nivolumab were listed, it would be included in the current risk-sharing agreement (RSA) for immunotherapy of NSCLC, with a minimal increase in the cap, and that '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' (para 7.20, nivolumab PSD, March 2023 PBAC meeting).
- 2.6 At its first consideration, the PBAC did not recommend the listing of nivolumab for the proposed indication, but considered that the outstanding issues could be resolved in a simple, early resubmission, with 'a price reduction that results in an [incremental cost-effectiveness ratio] ICER of not more than \$25,000 to < \$35,000 per [quality adjusted life year] QALY gained' and 'proposed parameters for revising the current RSA in place for immunotherapies for NSCLC to include neoadjuvant nivolumab' (para 7.21, nivolumab PSD, March 2023 PBAC meeting).
- 2.7 The resubmission was considered in July 2023. A price reduction from \$ [REDACTED] to \$ [REDACTED] per 100 mg resulted in a revised ICER of \$25,000 to < \$35,000 per QALY gained. The sponsor did not respond to the request to propose parameters for revision of the RSA in place for immunotherapies for NSCLC to include neoNIVO and uncertainties related to IO retreatment (para 1.2, Table 1, nivolumab PSD, March 2023 PBAC meeting).
- 2.8 At its second consideration, the PBAC noted that the revised financial estimates did not account for the existing and proposed restrictions for immune check-point inhibitors (ICIs) precluding use in relapsed or metastatic NSCLC and that this resulted in inaccurate estimates: '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' (paras 5.1, 5.9, nivolumab PSD, July 2023 PBAC meeting).
- 2.9 The PBAC also reiterated its view that, notwithstanding the acknowledgement that IO retreatment 'may be clinically appropriate', 'the resubmission did not provide evidence to support use of subsequent immunotherapy' so that 'use of immunotherapy in those who relapse with metastatic disease could not be supported by the Committee at this time' (para 5.3, nivolumab PSD, July 2023 PBAC meeting). For this reason, the restriction of treatment to three doses per lifetime was retained in the recommendation for listing.
- 2.10 The evaluation considered the resubmission's claim that 'there is a disconnect between the PBAC's recommended PBS restriction (which does not allow IO retreatment) and the PBAC's recommended economic evaluation (which allows IO retreatment)' is not justified, in that the PBAC did not recommend the inclusion of IO

retreatment in the economic model or accept the validity of the results when it was included.

- 2.11 In July 2023, the PBAC noted ‘that it would reconsider the recommendation to exclude retreatment in metastatic disease should evidence supporting such use become available’ (para 5.3, nivolumab PSD, July 2023 PBAC meeting).
- 2.12 The clinical claims remained as previously accepted by the PBAC (paras 4.10, 4.11, nivolumab PSD, July 2023 PBAC meeting): that neoNIVO+neoChemo has superior efficacy when compared with neoChemo. The claim of non-inferior comparative safety compared to neoChemo was not previously accepted by the PBAC and this decision was not challenged in the submission.

**Table 2: Summary of key matters of concern vs July 2023**

Matter of concern	Response	Addressed?
<b>Revision to the proposed restriction</b>		
The PBAC advised in July 2023 that due to a lack of clinical evidence repeat use of immunotherapy in those who relapse with metastatic disease could not be supported by the Committee. 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 (para 5.3, nivolumab PSD, July 2023 PBAC meeting).	The submission proposed two options for listing – Option A allowing retreatment; Option B not permitting retreatment. Option B includes a treatment criterion that is line with previous PBAC advice.	Yes
<b>Updated clinical effectiveness</b>		
The PBAC acknowledged that it would reconsider the recommendation to exclude retreatment in metastatic disease should evidence supporting such use become available (para 5.3, nivolumab PSD, July 2023 PBAC meeting).	The submission presented a literature search and a summary of publications reporting on the effectiveness of IO retreatment.	No – The evaluation considered the evidence provided was insufficient to establish either efficacy or effect size of retreatment.
<b>Updated financial estimates</b>		
The PBAC considered that utilisation was overestimated and the cost-offsets associated with current immunotherapy remained underestimated (para 5.11, nivolumab PSD, July 2023 PBAC meeting). Specific issues as listed: <ul style="list-style-type: none"> <li>• Additional atezolizumab patients should be removed. Should be captured in incident population for Stages II-IIIa.</li> <li>• Additional durvalumab patients should be removed. Should be captured in incident population for Stage III patient.</li> <li>• No repeated use of PD-L1 in metastatic setting.</li> <li>• Uptake of 30-40% per annum in the first 2 years of listing may be a more reasonable estimate of uptake.</li> </ul>	Updated estimates were provided for Option A and Option B.	<p>Yes</p> <p>Yes</p> <p>Option B - No.</p> <p>Addressed in PSCR.</p>
Calculation errors: Atezolizumab patients - 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. Durvalumab patients - The PBAC noted that in Year 1 only, the proportion considered unresectable applied was 15.6% instead of 20%.	Corrected.	Yes

Source: Constructed during the evaluation from the re-submission and the July PSD.

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; IO = immunotherapy; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1

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

### 3 Requested listing

3.1 The listing as proposed in the submission is shown below for Option A, that is allowing retreatment in metastatic disease. Revisions made by the sponsor to the restriction recommended by the PBAC in July 2023 are shown in italics and strikethrough.

MEDICINAL PRODUCT Form	PBS Item code	Max. Amount	No. of Rpts
NIVOLUMAB	New (Public) New (Private)	360mg	2
<b>Available brands</b>			
Opdivo (nivolumab 40mg/4mL injection , 4mL)			
Opdivo (nivolumab 100mg/mL injection, 10mL vial)			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospital			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)			
<b>Indication:</b> Resectable non-small cell lung cancer			
<b>Clinical criteria:</b>			
The condition must be at least one of: (i) node positive, (ii) at least 4 cm in size			
<b>AND</b>			
<b>Clinical criteria:</b>			
The treatment must be for neoadjuvant use in a patient preparing for surgical resection			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must have a WHO performance status of 0 or 1			
<b>AND</b>			
<b>Clinical criteria:</b>			
The treatment must be in combination with platinum-based chemotherapy			
<b>Treatment criteria:</b>			
Patient must not be undergoing treatment with more than 3 PBS-subsidised doses of this drug <del>per lifetime for this indication per neoadjuvant course of treatment</del>			
<b>Prescribing Instructions:</b>			
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.			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			

3.2 The sponsor proposed two PBS listing options, referred to as Option A and Option B. Option A, the sponsor’s preferred option, proposed modifying the recommended restriction to allow IO retreatment. Option B proposed not allowing IO retreatment and aligns with the listing recommended by the PBAC in July 2023. The submission proposed a special pricing arrangement (SPA). For Option A, the submission proposed an effective public hospital dispensed price for maximum amount (DPMA) of \$| (published \$7,191.10) and an effective private hospital DPMA of \$| (published \$7,333.82), updated since the previous submission for changes to applicable fees and mark ups. For Option B, the sponsor clarified in the Pre-Sub Committee Response (PSCR) that the proposed effective public hospital DPMA is \$| (published \$7,191.10)

and the effective private hospital DPMA proposed is \$1 (published \$7,333.82). The ESC noted that the proposed price increase for Option B resulted in effective prices that are higher than the proposed published prices. The ESC advised that this was not in keeping with current pricing procedures and was not appropriate.

- 3.3 The PBAC advised in July 2023 that repeat use of immunotherapy in those who relapse with metastatic disease could not be supported by the Committee due to a lack of clinical evidence to support such use. 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 (para 5.3, nivolumab PSD, July 2023 PBAC meeting). Option B includes the treatment criterion precluding IO retreatment recommended by the PBAC in July 2023. However, Option A amends the criterion to state 'Patient must not be undergoing treatment with more than 3 PBS-subsidised doses of this drug per neoadjuvant course of treatment', allowing for retreatment in the metastatic setting. The ESC considered the treatment criterion 'Patient must not be undergoing treatment with more than 3 PBS-subsidised doses of this drug per lifetime for this indication' in Option B may lead to leakage, as physicians may consider early stage resectable NSCLC as one indication and metastatic/unresectable NSCLC as another indication.
- 3.4 The proposed restriction for both Option A and Option B are otherwise aligned with the PBS listing recommended by the PBAC for nivolumab in July 2023, including a prescriber instruction stating that in non-squamous type NSCLC where an activating epidermal growth factor receptor (EGFR) gene mutation or anaplastic lymphoma kinase (ALK) gene rearrangement is detected, nivolumab must not be a PBS-benefit, and a PBS indication of 'non-small cell lung cancer' (para 5.3, nivolumab PSD, July 2023 PBAC meeting).
- 3.5 The Pre-PBAC Response proposed flow-on changes to IO listings in the metastatic setting for Option A restricting retreatment to patients who had not experienced disease progression while receiving neoadjuvant treatment or within 6 months of receiving neoadjuvant treatment. The Response proposed the inclusion of the following clinical criteria: 'Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for treatment of Stage IV (metastatic) non-small cell lung cancer' AND 'Patient must not have progressed while receiving nivolumab, or within 6 months of completing a course of nivolumab, for neoadjuvant treatment of resectable non-small cell lung cancer'. The Response argued that primary resistance to IO + chemotherapy requires adequate drug exposure (e.g. 6–8 weeks) and disease progression within

6 months of initiating therapy (Rizvi et al 2023; Tawbi et al 2023)<sup>2,3</sup>, and the proposed flow-on changes to IO listings in the metastatic setting would ensure cost-effectiveness of this regimen across the NSCLC treatment paradigm.

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

## **4 Consideration of the evidence for Option A (IO retreatment)**

### ***Sponsor hearing***

4.1 There was no hearing for this item.

### ***Consumer comments***

- 4.1 In addition to the input noted by the PBAC at the March 2024 meeting (paras 6.2, 6.3, nivolumab PSD, March 2023 PBAC meeting) and the July 2023 meeting (paras 4.2, 4.3, nivolumab PSD, July 2023 PBAC meeting), the PBAC noted and welcomed the input from health care professionals (12) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with nivolumab for neoadjuvant treatment of NSCLC.
- 4.2 Comments from health care professionals described support for the listing of nivolumab for neoadjuvant treatment of resectable NSCLC. The PBAC noted such a listing was recommended at the July 2023 meeting.
- 4.3 The comments from health care professionals further focused on access and equity, expressing concern for those patients who may be ineligible for later immunotherapy should they not respond to treatment or relapse. The comments stated that three cycles should not constitute a 'course' of immunotherapy, and thus a lifetime restriction should not be applied to those who undergo treatment.
- 4.4 The input from Lung Foundation Australia described the burdens that lung cancer places on Australian society and stated it supported a nivolumab listing that allows IO retreatment.
- 4.5 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the nivolumab submission. MOGA stated that it strongly supported the amendment to the requested listing to ensure patients with recurrent lung cancer, who have received immunotherapy for curative intent, are able to have access to nivolumab at the time of recurrence.

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<sup>2</sup> Rizvi, N., et al (2023). Society for Immunotherapy of Cancer (SITC) consensus definitions for resistance to combinations of immune checkpoint inhibitors with chemotherapy. *Journal for Immunotherapy of Cancer*, 11(3), 5920.

<sup>3</sup> Tawbi, H., et al (2023). Society for Immunotherapy of Cancer (SITC) checkpoint inhibitor resistance definitions: Efforts to harmonize terminology and accelerate immuno-oncology drug development. In *Journal for Immunotherapy of Cancer* (Vol. 11, Issue 7, p. e007309). *BMJ Specialist Journals*.

## **Clinical studies**

- 4.6 The submission sought to provide evidence supporting IO retreatment. It provided a clinical rationale for retreatment and publications from a literature search (see paragraph 4.10 onwards below).
- 4.7 The evaluation considered that the best source of evidence to support retreatment with IO in the metastatic setting would be long-term follow up data from the trial, Checkmate 816, on which the decision to list nivolumab as neoadjuvant treatment was based, which allowed patients who received nivolumab or placebo and whose tumours recurred to receive immunotherapy. However, the submission stated that of 179 patients treated with neoNIVO, 15 had received IO retreatment for recurrence, but that '[e]fficacy data on these retreated patients is immature at this time and not available to the Sponsor'.
- 4.8 Given that data from a study of similar design is relevant to the use of PD-L1 inhibitor retreatment in melanoma,<sup>4</sup> the PBAC may wish to consider whether awaiting the outcome of this data from Checkmate 816 would be appropriate. The ESC agreed with the evaluation that long-term follow up data from the trial would be an ideal source of evidence to support retreatment with IO in the metastatic setting.
- 4.9 The submission presented data obtained by a targeted literature search in Embase. The search terms were 1: 'immunotherapy OR nivolumab OR pembrolizumab' 2: 'retreatment OR rechallenge', 3: 'NSCLC OR non-small cell lung cancer', with studies reviewed being '1 AND 2 AND 3'. This search identified 242 studies, of which 53 were included in the submission.
- 4.10 The included studies were briefly detailed in the submission. None of the studies included patients receiving nivolumab as neoadjuvant treatment for resectable disease and then relapsing. The submission nominated 18 studies as representing the primary evidence for IO retreatment. These studies are shown in Table 3 below.
- 4.11 Eleven of the 18 studies were retrospective case series, and therefore had a high risk of bias. One was a Phase II, single arm trial, and also had a high risk of bias. Five studies were described as systematic reviews or meta-analyses. Three studies (Bozorgmehr 2023; Giaj Levra 2020; Rodriguez-Abreu 2022) were analyses of selected trials and database records; Bozorgmehr 2023 included the data from Giaj Levra 2020 and some of the data from Rodriguez-Abreu 2022. The data reported in Rodriguez-Abreu 2022, and most of the data reported by Bozorgmehr 2023 when that of Giaj Levra 2020 is excluded, were for pembrolizumab.
- 4.12 The evaluation considered that the most salient data was that reported in Giaj Levra 2020. This study reported data from 10,452 patients recorded in a French national

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<sup>4</sup> Eggermont AMM, Mescheryakov A, Atkinson V, et al. Crossover and rechallenge with pembrolizumab in recurrent patients from the EORTC 1325-MG/Keynote-054 phase III trial, pembrolizumab versus placebo after complete resection of high-risk stage III melanoma. *Eur J Cancer* 2021; 158:156-168.

database as starting nivolumab for locally advanced or metastatic lung cancer during 2015–2016. Nivolumab was discontinued in 9593 (91.8%) patients, of whom 5118 (53.3%) subsequently received systemic treatment, which was chemotherapy only in 3607 (70.4%), nivolumab in 1499 (29.3%) and pembrolizumab in 18 (0.4%). Median survival on retreatment with a PD-L1 inhibitor was longer than in the cohort as a whole (IO resumption group = 14.8 months [95% confidence interval [CI] 13.4, 16.5], IO rechallenge group = 18.1 months [95% CI: 14.6, 21.6], versus overall group = 11.5 months [95% CI: 11.1, 11.9]), however survival of patients retreated with chemotherapy only was not reported. There was a strong association between survival on IO retreatment and the duration of initial nivolumab treatment. For the IO resumption group, the hazard ratio for death was 0.19 (95% CI 0.14, 0.25) for initial IO treatment greater than 6 months compared to 0.56 (95% CI 0.46, 0.70) for patients initially treated with IO for less than 3 months. The duration of proposed adjuvant use of nivolumab is less than three months, but in the locally advanced or metastatic setting a short duration of initial treatment may be a marker for poor response or intolerance.

- 4.13 Expert opinion presented to the PBAC in March 2023 stated that the use of PD-L1 inhibitors in patients with recurrence is reasonable in patients who have received nivolumab as neoadjuvant treatment for resectable NSCLC (para 6.1, nivolumab PSD, March 2023 PBAC meeting). The data provided in the submission did not include patients receiving neoadjuvant treatment for resectable disease and did not report an estimate for the magnitude of benefit associated with IO retreatment, therefore the evaluation considered that the PBAC's view in March 2023 that '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' (para 7.20, nivolumab PSD, March 2023 PBAC meeting) remains relevant.
- 4.14 The PSCR acknowledged that the clinical data presented in the submission was not specific to patients receiving nivolumab as neoadjuvant treatment for resectable disease and then relapsing and receiving metastatic IO. However, the sponsor considered that the available clinical evidence in combination with a strong biological rationale and a limited proportion of patients who progressed on treatment in the CheckMate 816 trial supported retreatment in this circumstance.
- 4.15 The ESC considered that, overall, the newly presented studies were not reliable for decision-making. The studies were considered inadequate to support the sponsor's preferred restriction ('Option A').
- 4.16 The Pre-PBAC Response argued that there is biological rationale and clinical evidence to support that patients who do not progress on treatment or within 6 months of completing treatment will remain sensitive to future treatment with IO (Gonzalez et

al., 2018; McGranahan et al., 2016)<sup>5,6</sup>. The Response noted that the evidence included in the submission primarily supported IO retreatment for patients who have stopped initial IO therapy for one of three reasons: 1) completion of course of therapy; 2) cessation of treatment due to adverse events; or 3) a personal decision to stop treatment. The Response therefore proposed flow-on changes to IO listings in the metastatic setting for Option A restricting retreatment to patients who had not experienced disease progression while receiving or within 6 months of receiving neoadjuvant treatment (see paragraph 3.5). The Response considered the proposed changes to the restriction wording in the metastatic setting would support the use of IO retreatment in patient groups likely to achieve the best possible clinical outcomes.

**Table 3: Summary table of cited evidence for immunotherapy retreatment or rechallenge in NSCLC**

Author	Publication	N	Study	Data Summary
Bozorgmehr et al (2023)	Review	-	Summary of 17 studies	<p>Trials with a restricted treatment duration of 2 years were summarised with a focus on those who completed 2 years with either pembro or nivo (+/- chemo), then were rechallenged after progression. Up to 25% patients successfully completed 2 years of initial IO therapy.</p> <p>KN010: 79 patients completed 2 years of pembro. 21/79 received a second course of pembro, DCR 81% (1 achieving CR, 10 receiving PR, 6 with SD).</p> <p>KN024: 39 patients completed 2 years of pembro. 12 patients received a second course of pembro. DCR 83.3% (4 PRs and 6 SDs).</p> <p>KN042: 33 patients received a second course of pembro. DCR 76.0% (5 PRs and 20 SDs).</p> <p>Bernard-Tessier 2018: PR for 2 patients and SD for 6 patients after rechallenge.</p> <p>Sheth et al: 168 patients completed 12 months of durva treatment (various solid tumours). 70 patients were rechallenged on progression. 21 NSCLC patients received a DCR of 52.4% (3 PRs, 14%). 70% overall experienced clinical benefit.</p> <p>Gobbini 2020: Retrospectively explored 144 NSCLC patients with ICI rechallenge, 16% ORR on second course, PFS was 5.1 or 6.5 months for patients discontinuing first ICI due to toxicity or clinical decision, reactively.</p> <p>Levra et al: 10,452 nivolumab treated patients from a national database were identified. 1,517 had received a second course of ICI. The outcome was significantly better in patients with a long initial nivo duration of treatment.</p> <p>DICIPLE: first trial to systematically evaluate ICI resumption after treatment discontinuation. 6 months of NIVO+Ipi followed by ICI resumption in case of progression (stop and go) was compared to continuous NIVO+Ipi. Lower PFS in the continuation group compared with stop and go (20.8 vs 35.2 months) although not statistically significant due to small patient numbers (n=32).</p>

<sup>5</sup> Gonzalez, H., Hagerling, C., & Werb, Z. (2018). Roles of the immune system in cancer: From tumor initiation to metastatic progression. In *Genes and Development* (Vol. 32, Issues 19–20, pp. 1267–1284).

<sup>6</sup> McGranahan, N., et al (2016). Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science*, 351(6280), 1463–1469.

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Author	Publication	N	Study	Data Summary
Cai et al (2022)	Article	-	Meta-analysis	18 studies were enrolled. The pooled ORR and DCR of ICI retreatment were 20% and 54%, respectively. The pooled ORR and DCR of ICIs rechallenge (classified as retreatment upon progression) were 8% and 39%, respectively. ICIs resumption presented an ORR of 34% and a DCR of 71%. The meta-analysis suggested retreatment with ICIs is feasible for patients with NSCLC in consideration of encouraging efficacy and safety, especially in resumption with ICIs (patients who discontinued prior treatment due to irAE or completion of a fixed dose of ICI).
Giaj Levra et al (2020)	Article	10,452	Retrospective analysis of database	10,452 patients were identified who had received nivo treatment. During initial treatment with nivo, median DoT was 2.8 months. Median OS was 11.5 months. Following discontinuation with nivo, 5118 received at least one other systemic therapy; 1517 received a further course of nivo or pembro. This was started without any intervening chemo in 1127 patients or following an intervening chemo group (390 patients). Of 1127 patients in the 'resumption' group, median DoT was 4 months and median OS2 (OS from the start of retreatment with a PD-1 inhibitor) was 14.8 months. Of 390 patients in the 'rechallenge' group, median DoT was 3.0 months and median OS2 was 18.1 months. For all patients who had a second course of ICI, OS2 was longest in patients who had been treated the longest during the initial nivo course.
Gobbini et al (2020a)	Article	144	Retrospective observational multicentre study	This study reports on 144 advanced NSCLC patients whose disease was rechallenged with ICIs after more than 12 weeks of discontinuation. PFS on rechallenge was 4.4 (95% CI: 3–6.5) months and OS on rechallenge was 1.5 (95% CI: 1.0–2.1) years. Longer PFS and OS on rechallenge was observed for patients who discontinued their first ICI due to toxicity or clinical decision (i.e. not progression), those not receiving systemic treatment between ICIs and those with a good ECOG score at the time of rechallenge.
Gobbini et al (2020b)	Article	74	Meta-analysis	14 papers including 74 patients were included. 39 (53%) of the patients had NSCLC. Higher objective response and DCRs were obtained upon first ICI treatment compared to rechallenge. 15% of patients with NSCLC had a PR on rechallenge and 23% had SD. A longer PFS was observed in patients who discontinued the first ICI due to toxicity or per protocol and in those not receiving intercalated treatment between the two ICIs.
Miura et al (2022)	Abstract	61	Phase II trial single-arm	Advanced NSCLC patients who had previous clinical benefit (CR/PR/SD over 6 months) from previous ICI (+/- chemo) received nivo 240mg q2w until progression. Overall nivo had a 8.5% ORR (95% CI: 2.8–18.7%) and 2.6 months median PFS (95% CI: 1.6–2.8). A small group of 5 responders demonstrated durable 11.1 months of median PFS.
Mouri et al (2019)	Article	21	Retrospective single centre analysis	49 out of 187 patients treated with nivo experienced an irAE. Retreatment was chosen in 21 patients while 28 patients discontinued. Retreatment with nivo showed an overall response rate of 15%. Retreatment exhibited a slightly higher efficacy without a significant increase in irAEs.

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Author	Publication	N	Study	Data Summary
Nan et al (2020)	Abstract	19	Retrospective single centre study	44 patients discontinued due to an irAE, of which 19 were rechallenged with the same or a different ICI. 42% of patients had PR or SD upon rechallenge, 58% had progression of disease.
Park et al (2020)	Article	-	Systematic review and meta-analysis	The meta-analysis assessed rechallenge after patients experienced an irAE. In total, 10 studies comprising of 649 patients and 437 patients who had subsequent rechallenge were identified. NSCLC consisted of 33% of these studies. Overall, the meta-analysis suggested rechallenge following treatment cessation due to irAEs is safe and efficacious. The evaluation considered that the evidence appeared to be strongest for rechallenge with monotherapy ICI in the setting of irAE due to initial combination therapy.
Perdyan et al (2023)	Article	-	Systematic review	In total, 31 articles were included with a total of 812 cancer patients. There were 16 retreatment and 13 rechallenge studies. Fifteen studies reported improvement or maintenance of overall response or disease control rate at the secondary treatment. The study suggested interval treatment, primary response to ICIs and the cause of cessation from the primary ICI were likely to be predictors of secondary response to ICIs.
Plazy et al (2022a)	Article	-	Systematic review	Not NSCLC specific; investigated reintroduction of ICIs after disease progression (rechallenge) or irAEs (resumption). Heterogenous results across rechallenge studies with overall response rate 0–54%, PFS 1.5–12.9 months and OS 6.5–23.8 months. Better outcomes were recorded in patients with good ECOG PS, longer duration of initial ICI, discontinuation reason of initial ICI other than progression and those who received ICI sequence other than switch between anti-PD-1 and anti-PD-L1.
Plazy et al (2022b)	Abstract	81	Retrospective single centre study	187 patients received at least 1 line of ICI. Patients were divided into rechallenge (n=81) and not rechallenged (n=106). Reason for first discontinuation was not clear. Patients in the rechallenged group had a higher OS since first ICI compared to the not rechallenged group (39.7 months vs 13.3 months), p<0.0001).
Rodriguez-Abreu et al (2022)	Abstract		Pooled analysis	Patients whose disease progressed after completing 2 years of pembro were eligible to receive a second course of pembro. This analysis pooled patients with pembro monotherapy (cohort 1) in KN024, KN042 and KN598 and also pembro plus chemo in KN189 and KN407 (cohort 2). Patients included received up to 1 year of pembro monotherapy after either receiving 2 years of pembro initially or stopping due to CR. In cohort 1, 58/148 received a second course of pembro. 16/55 patients were in cohort 2. ORR during second course pembro was 19% in cohort 1 and 6% in cohort 2. Overall, the evaluation considered that the data supported pembro retreatment upon PD.
Santini et al (2018)	Article	38	Retrospective single centre analysis	Out of 482 NSCLC patients treated with anti-PD-L1, 68 (14%) developed a serious irAE requiring treatment interruption. Of these, 38 (56%) were retreated and 30 (44%) had treatment discontinued. Among those with no PRs prior to the irAE, PFS and OS were longer in the retreatment cohort. Conversely, for those with objective responses prior to the irAE, PFS and OS were similar in the retreatment and discontinuation cohorts.
Takahara et al (2022)	Article	24	Retrospective observational study	24 patients diagnosed with NSCLC and rechallenged with ICIs were followed. With regard to reason for discontinuation of initial ICIs: responder group 8 patients had PD and 4 had irAE; non

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Author	Publication	N	Study	Data Summary
				<p>responder group 9 patients had PD, 3 irAEs and one due to clinician discretion.</p> <p>11 were in the responder group (those who had CR, PR or SD) and 13 in the non responder group (those who had PD). In the responder group, 2 patients had PR and 9 had SD. The response rate was 8.3% and DCR was 45.8%.</p> <p>The study suggested that rechallenge with ICIs can provide long-term disease control and prolonged prognosis with continued treatment, even if tumour growth within the SD range is observed in the initial response assessment. Additionally, rechallenge with ICIs should be a treatment option, even in patients with characteristics that might cause non-response to ICIs.</p>
Tam et al (2018)	Abstract	16	Retrospective cross-sectional study	<p>176 eligible patients with metastatic melanoma or NSCLC, 25 patients experienced an irAE and 16 were rechallenged upon resolution. Post rechallenge, 25% progressed on subsequent scan, 6.3% demonstrated regression, 25.0% remained stable with ongoing ICI; 31.3% were stable on surveillance and 12.5% died prior to repeat scans.</p> <p>This study suggested that rechallenge with ICI post-grade III/IV irAE may not be associated with recurrence of irAE. Durability of response post-rechallenge was demonstrated in 64.2% of patients with SD on an ICI or surveillance.</p>
Torasawa et al (2023)	Article	64	Retrospective analysis from single centre	<p>Patients who received ICI retreatment were divided into two groups – those who had disease progression while on ICI treatment and those without PD (i.e. progressed afterwards). 30 of 64 patients were in the PD group and 34 in the no PD group. Patients in the no PD group had better clinical outcomes than those in the PD group (ORR 29.4% vs 6.7%, p =0.03; median PFS 4.1 vs 2.2 months, p=0.07). ICI rechallenge was more successful than retreatment in those who had progressed on therapy previously.</p>
Xu et al (2022)	Article	40	Retrospective cohort study	<p>The study only included patients who had discontinued initial ICI treatment due to PD and were retreated. Median PFS of patients receiving an initial ICI was 5.7 months. Median PFS for retreatment was 6.8 months.</p> <p>Tendencies for longer PFS were observed in non-smokers or patients with adenocarcinoma, response of stable/progressive disease in initial immunotherapy, or whose treatment lines prior to ICI rechallenge were one/two.</p> <p>The study suggested that retreatment may be an option for NSCLC after progression on first ICI.</p>
Yang et al (2022)	Article	81	Retrospective cohort study	<p>Patients were enrolled with advanced NSCLC who received an ICI and discontinued due to irAEs or disease progression. The R group achieved better OS than the NR group (HR=0.176, p=0.001). In the irAEs group, survival analysis showed a trend toward improved OS in the rechallenge subgroup (HR=0.287, p=0.055) and a DCR of 75% after an ICI rechallenge.</p> <p>In the disease progression group, the rechallenge subgroup did not improve OS (HR=0.214, p=0.144) and the DCR of the rechallenge subgroup was 40% after ICI rechallenge.</p> <p>The study suggested that an ICI rechallenge may be an clinically beneficial option for patients who discontinue treatment due to irAEs.</p>

Source: modified during the evaluation from the submission

chemo = chemotherapy; CI = confidence interval; CR = complete response; DCR = disease control rate; DoT = duration of treatment; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; ICI = immune checkpoint inhibitor; Ipi = ipilimumab; IO = immunotherapy; irAE = immune-related Adverse Event; NSCLC = non-small cell lung cancer; nivo = nivolumab; NR = non-rechallenge; ORR = objective response rate; OS = overall survival; PR = partial response; pembro = pembrolizumab; PD = progressive disease; PFS = progression free survival; PFS1 = progression free survival 1 (time to first progression); PFS2 = progression free survival 2 (time to second progression); PS = performance status; q2w = once every two weeks; R = rechallenge; SD = stable disease; TTF = time to treatment failure.

### **Comparative effectiveness and safety**

- 4.17 No comparative evidence was presented to support retreatment with a PD-L1 inhibitor versus an alternative treatment.

### **Economic analysis for Option B (no IO retreatment, price increase)**

- 4.18 The PBAC previously considered nivolumab to be acceptably cost-effective, based on the economic model included in the July 2023 resubmission. The PBAC considered the re-specified base case was acceptable which incorporated a 15 year time horizon, event-free survival (EFS) and locoregional recurrence (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. The PBAC previously noted that the re-specified base case did not incorporate an onset of cure of 6 years in the nivolumab + chemotherapy arm and 5 years in the chemotherapy arm, however the PBAC considered that the data from Interim analysis 2 of the Checkmate 816 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 July 2023 resubmission addressed previous concerns regarding the cost-effectiveness of nivolumab (para 5.7, nivolumab PSD, July 2023 PBAC meeting).
- 4.19 The current submission stated that while immunotherapy retreatment was not supported by the PBAC in July 2023, the accepted economic model included immunotherapy retreatment. The current submission therefore argued that if the economic model was to align with the recommended PBS restriction precluding IO retreatment that ‘the recommended price for nivolumab would not reflect cost-effectiveness of use in this setting’. The submission stated that if IO retreatment is precluded then the unit price for nivolumab should be higher to maintain an ICER of \$25,000 to < \$35,000 per QALY gained. The current submission therefore presented two economic models. The economic model for Option A included IO retreatment and was unchanged from the model considered by the PBAC in July 2023 (Table 5). The economic model for Option B precluded IO retreatment and increased the price of nivolumab from \$| per 100 mg vial to \$| per 100 mg vial, resulting in an ICER of \$25,000 to < \$35,000 per QALY gained. The ESC advised that the ICER of \$25,000 to < \$35,000 per QALY gained was accepted by the PBAC in July 2023 under the assumption that IO retreatment would be precluded. In consideration of the cost-effectiveness of neoadjuvant nivolumab and IO retreatment, given the uncertainty related to the clinical and modelled benefits associated with IO retreatment, a lower ICER may be more appropriate.

4.20 The key inputs to the economic models previously considered by the PBAC and the updated changes in this resubmission are summarised in Table 4 below.

**Table 4: Summary of changes to the economic model.**

Parameter	March 2023 Submission	July 2023 submission	March 2024 submission	
			Option A	Option B
Time horizon	25 years	15 years	15 years	
Onset of cure	5 years (both treatment arms)	6 years (both treatment arms)	6 years (both treatment arms)	
Utility values	Trial-based utilities from CheckMate 816	EFS and LR health state utilities from Grutters et al (2010)	EFS and LR health state utilities from Grutters et al (2010)	
Nivolumab ex-manufacturer price (100 mg)	\$█	\$█	\$█	\$█
Immunotherapy retreatment	Permitted	Permitted	Permitted	Not permitted
ICER/QALY gained	\$█ <sup>1</sup>	\$█ <sup>1</sup>	\$█ <sup>1</sup>	\$█ <sup>1</sup>

Source: Tables 4 and 5 pp, 22 and 23 of the submission.

EFS = event free survival; LR = locoregional

The redacted values correspond to the following ranges:

<sup>1</sup>\$25,000 to < \$35,000

4.21 It was noted during the evaluation that the economic models presented in the submission did not include updated pharmacy fees and mark-ups. When correcting the models for these costs, the ICER increases from \$25,000 to < \$35,000 per QALY gained in the Option A model and \$25,000 to < \$35,000 per QALY gained in the Option B model.

4.22 Table 5 summarises the stepped changes made to the economic models.

**Table 5: Stepped changes made to the economic model: Option A/July 2023 to Option B model**

Step		Nivo cost	Chemo cost	Nivo QALY	Chemo QALY	Inc. cost	Inc. QALY	ICER(\$)
	Base case ICER of the July 2023 resubmission model (Option A)	\$█	█	4.18	3.52	\$█	0.66	█ <sup>1</sup>
1	+ Removal of immunotherapy retreatment	\$█	█	4.02	3.52	\$█	0.51	█ <sup>2</sup>
2	+ Nivolumab price increased to \$█ per 100 mg vial (Option B)	\$█	█	4.02	3.52	\$█	0.51	█ <sup>1</sup>
3	+ Updated pharmacy mark-ups and fees (aligned with the financial estimates model)	\$█	█	4.02	3.52	\$█	0.51	█ <sup>1</sup>

Source: constructed during the evaluation.

chemo= chemotherapy; ICER = incremental cost-effectiveness ratio; inc. = incremental; nivo = nivolumab

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$15,000 to < \$25,000

4.23 Sensitivity analyses were not provided in the submission. Key sensitivity analyses were conducted during the evaluation for the Option B model and are shown in Table 7.

- 4.24 The economic model included four health states: EFS, LR, distant metastasis (DM) and death. The DM health state was modelled as an absorbing health state, where one-off costs, life years (LYs) and QALYs assumed to be associated with developing a distant metastasis were applied on transition into the health state. In the economic model considered by the PBAC in July 2023 (also Option A model), the health outcomes associated with various treatments for metastatic NSCLC applied to the DM health state were based on the previous PBAC submissions of pembrolizumab combination therapy (pembrolizumab PSDs, November 2018 and July 2019 PBAC meetings), and then weighted by the proportion of patients receiving each therapy (Table 6). In the Option A model, patients in the DM health state that previously received nivolumab were assumed to receive pembrolizumab (28%), pembrolizumab + platinum doublet chemotherapy (PDC) (42%), PDC alone (15%) or best supportive care (15%). The same percentages were assumed for patients progressing in the neoChemo arm of both models. In the Option B model, patients in the DM health state that previously received nivolumab were assumed to receive PDC (85%) and best supportive care (15%) (Table 6). The ESC recalled that the previous November 2018 and July 2019 PBAC submissions for pembrolizumab were for the consideration of treatment for IO naïve patients. Therefore, the ESC considered that while these data may be applicable to the DM health state for the neoChemo arm, there remained uncertainty related to whether the same benefit observed in these data would be observed for patients subsequent to receiving nivolumab.
- 4.25 The ESC recalled it had previously considered that applying one-off discounted LYs, QALYs and costs on transition into the DM health state may be oversimplistic as it does not account for the relationship between transitions, costs, and the health outcomes associated with metastatic disease. The ESC recalled it had also previously expressed concern that the one-off costs and outcomes are predominately independent to the time horizon, so that if the time horizon is reduced it has little impact on the cost and health outcomes associated with the DM health state. The ESC reiterated that a model structure that incorporates transitions from a distant metastasis health state to death is the preferred modelling approach. The PBAC also previously considered that modelling the DM health state as an absorbing state in which cost-ineffective therapies were applied contributed to the structural uncertainty of the model (paras 6.77, 7.13, nivolumab PSD, March 2023 PBAC meeting).
- 4.26 The ESC noted that this aspect of the model continued to be a key driver of uncertainty in the model. Aside from the cost of nivolumab, the chief difference between the economic model for Option A and B relies on the assumed difference in one-off costs and health outcomes associated with metastatic treatment options (IO vs no IO; see Table 6 below) applied on transition to the DM health state. The ESC reiterated its previous advice and the advice of the PBAC that the assumed cost-effectiveness of these treatments and their application in the model were not appropriate.
- 4.27 Removing IO retreatment for metastatic disease in the Option B model is assumed to reduce the quality adjusted life years applied to patients compared to neoChemo

patients who recur with distant metastases and receive IO. In the base case, the QALYs assigned to these patients on transition to the DM health state reduces from 1.357 to 0.887. Similarly, the cost associated with this treatment is reduced, from \$[redacted] to \$[redacted]. These differences are large and represent the difference in QALYs and costs for each first line metastatic treatment and their assumed market share across the treatment arms for the DM health state (see Table 6 below). The cost and health outcomes assumed for each first line metastatic treatment has previously been considered by the ESC to not be well justified (paras 6.73–6.75, Table 18, nivolumab PSD, March 2023 PBAC meeting). These assumptions are tested in sensitivity analyses (Table 7). The ESC noted that the Option B model (no IO retreatment) was sensitive to changes to the assumptions associated with the assumed one-off costs and health benefits of IO treatment assigned to the neoChemo arm of the model. The ESC noted plausible changes in either the assumed costs or benefits resulted in ICERs of approximately \$45,000 to < \$55,000 per QALY gained.

**Table 6: Distribution of different NSCLC therapies for metastatic disease, with weighting differences between the options**

	Pembrolizumab	Pembrolizumab + PDC (squamous)	Pembrolizumab + PDC (non-squamous)	PDC	BSC	Weighted
Total cost	\$[redacted]	\$[redacted]	\$[redacted]	\$50,157	\$26,028	
QALYs	1.81	0.84	1.57	0.90	0.81	
LYs	2.55	1.15	2.1	1.24	1.12	
<b>Option A: NeoNIVO+NeoChemo and NeoChemo treatment arms</b>						
<b>Option B: NeoChemo treatment arm</b>						
Distribution	28.32%	9.42%	32.62%	14.64%	15%	–
Total cost						\$[redacted]
QALYs						<b>1.357</b>
LYs						<b>1.87</b>
<b>Option B: NeoNIVO</b>						
Distribution	0.00%	0.00%	0.00%	85.00%	15.00%	
Total cost						\$[redacted]
QALYs						<b>0.887</b>
LYs						<b>1.22</b>

Source: Updated from Table 19, nivolumab PSD, March 2023 PBAC Meeting and 'Attachment 3 - Nivolumab Neoadjuvant NSCLC Economic Evaluation\_No Retreatment\_Nov23.xlsm'

BSC = best supportive care; NSCLC = non-small cell lung cancer; LYs = life years; PDC = platinum-doublet chemotherapy; QALYs = quality-adjusted life years

Table 7: Key sensitivity analyses, Option B

Variables altered in sensitivity analysis	Incremental costs	Incremental QALYs	ICER	% change from base case
<b>Base case results<sup>a</sup></b>	\$█	0.51	\$█ <sup>1</sup>	-
<b>Discount rate (base case = 5.0% per annum)</b>				
0.0%	\$█	0.78	\$█ <sup>2</sup>	- █%
3.5%	\$█	0.58	\$█ <sup>1</sup>	- █%
<b>One-off weighted costs applied to DM for IO treatment in NeoChemo arm (base case = \$█)</b>				
\$█	\$█	0.51	\$█ <sup>3</sup>	+ █%
\$█	\$█	0.51	\$█ <sup>4</sup>	- █%
<b>One-off weighted QALYs applied to DM for IO treatment in NeoChemo arm (base case = 1.357)</b>				
1.00	\$█	0.66	\$█ <sup>2</sup>	- █%
1.80	\$█	0.31	\$█ <sup>3</sup>	+ █%
<b>Cost of nivolumab (base case = \$█ per 100 mg, ex-manufacturer price)</b>				
\$█ per 100 mg	\$█	0.51	\$█ <sup>2</sup>	- █%

Source: constructed during the evaluation with 'Attachment 3 - Nivolumab Neoadjuvant NSCLC Economic Evaluation\_No Retreatment\_Nov23.xlsm'

DM = distant metastasis; ICER = incremental cost-effectiveness ratio; IO = immunotherapy; QALYs = quality adjusted life years

<sup>a</sup> Updated pharmacy mark-ups and fees (aligned with the financial estimates model).

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$15,000 to < \$25,000

<sup>3</sup> \$45,000 to < \$55,000

<sup>4</sup> \$5,000 to < \$15,000

### Cost per patient per course

Table 8: Drug cost per patient for proposed and comparator drugs, Option A and B

	Nivolumab			Chemotherapy		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose	NIVO 360mg Q3W + chemo Q3W <sup>a</sup>	NIVO 360 mg Q3W + chemo Q3W <sup>a</sup>	NIVO 360 mg Q3W + chemo Q3W <sup>a</sup>	chemo Q3W <sup>a</sup>	chemo Q3W <sup>a</sup>	chemo Q3W <sup>a</sup>
Mean number of 3-week cycles	2.91 <sup>b</sup>	2.99	NIVO: 2.91 Chemo: 2.63–2.93	2.71 <sup>c</sup>	2.99	2.48–2.86
Cost per 3-week cycle	Option A neoNIVO+neoChemo = \$■+\$■ Option B: neoNIVO+neoChemo = \$■+\$■	Option A: neoNIVO+neoChemo = \$■+\$■ Option B: neoNIVO+neoChemo = \$■+\$■	Option A: neoNIVO = \$■ Option B: neoNIVO = \$■	\$418	\$418	Not reported
Cost/patient/course	\$■	Option A: neoNIVO+neoChemo = \$■+\$■ Option B: neoNIVO+neoChemo = \$■+\$■	Option A: neoNIVO = \$■ Option B: neoNIVO = \$■	\$1,133	\$1,250	Not reported

Source: Table constructed during the evaluation, based on Table 24, nivolumab PSD, March 2023 PBAC meeting  
chemo = chemotherapy; NIVO = nivolumab; Q3W = every 3 weeks

<sup>a</sup> The dosing of chemotherapies vary across agents. The dose regimens for chemotherapies used in the economic model were sourced from the key Trial CM816 and were generally consistent with the Australian treatment guidelines and product information documents.

<sup>b</sup> Mean number of treatment cycles for nivolumab calculated based on data provided in Table 6.1-1, p91 of the clinical study report of Trial CM816. The number of treatment cycles for chemotherapy agents were slightly different from that for nivolumab.

<sup>c</sup> Mean number of cycles for cisplatin calculated based on data provided in Table S.4.1.1, p111 of "CheckMate 816 Supplement tables". The number of treatment cycles for other chemotherapy agents were slightly different from that for cisplatin.

### Estimated PBS usage & financial implications

4.28 This submission was not considered by DUSC.

4.29 In July 2023, the PBAC noted that the financial estimates would be acceptable once corrected for the errors identified (paras 4.22, 4.23, nivolumab PSD, July 2023 PBAC meeting), the additional atezolizumab and durvalumab patients were removed (para 5.8, nivolumab PSD, July 2023 PBAC meeting), the cost-offsets were updated to assume no repeat use of immunotherapy for metastatic disease (para 5.9, nivolumab PSD, July 2023 PBAC meeting), a 30–40% uptake of nivolumab in the first two years of listing (para 5.9, nivolumab PSD, July 2023 PBAC meeting) and effective prices were incorporated.

4.30 The current submission provided revised financial estimates that included the following amendments:

- Two sets of financial estimates were provided, one for Option A (allowing IO retreatment) and one for Option B (no IO retreatment allowed). For Option A, an effective approved ex-manufacturer price (AEMP) of \$■ per 100 mg vial was applied. This is unchanged from the previous submission. For Option B, an

effective AEMP of \$| per 100 mg vial was also applied. This was an error identified by the evaluation. The effective price for nivolumab applied to the financial workbook for Option B was corrected in the PSCR to an effective AEMP of \$| per 100 mg vial. Tables herein incorporate the corrected AEMP.

- Correction of calculation errors related to atezolizumab and durvalumab patients previously identified (paras 4.22, 4.23, nivolumab PSD, July 2023 PBAC meeting).
  - The additional atezolizumab and durvalumab patients were removed (para 5.8, nivolumab PSD, July 2023 PBAC meeting).
  - Metastatic cost offsets were estimated based on 21% of neoNIVO+neoChemo patients not experiencing distant metastases or recurrence in the Option A financial estimates. This is unchanged from the previous submission. For Option B, this estimate was increased to 29%. The PSCR incorrectly increased the percentage to 50% for the Option A model whereas it should have been increased to 50% for the Option B model (see paragraph 4.31).
  - Fees and markups were updated to reflect the costs as at November 2023.
- 4.31 The PBAC previously considered that the reduced use of immunotherapy for metastatic disease should be incorporated in the financials, and that this may be achieved by using the approach 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 and not receiving repeat immunotherapy (paras 5.9, 5.11, nivolumab PSD, July 2023 PBAC meeting). Consistent with the previous submission, the assumed cost-offset associated with the reduced use of immunotherapy in the metastatic setting was based on data from the assessment of time to distant metastases (TTDM) reported from the 3-year update of the CM816.
- 4.32 For Option A, the submission continued to assume a 21% reduction in distant metastases and subsequent metastatic immunotherapy costs associated with the treatment of neoNIVO compared with neoChemo. The ESC considered that this was appropriate, however the PSCR increased this percentage to 50%. This was considered to be an error and is not reflected in the financials presented herein.
- 4.33 For Option B, the submission assumed that 29% of neoNIVO+neoChemo patients would develop distant metastases (or died) but would not be eligible for a course of PBS-listed immunotherapy for metastatic disease. This percentage was unchanged in the PSCR. The submission therefore assumed that there would be no cost-offset associated with a 21% reduction in distant metastases associated with the treatment of neoNIVO compared with neoChemo in Option B. This is not aligned with previous PBAC advice (paras 5.9, 5.11, nivolumab PSD, July 2023 PBAC meeting). The PSCR stated that the sponsor was unclear of the methodology applied to determine the PBAC's advice regarding cost-offsets due to reduced immunotherapy use (50%). The PSCR considered that it was unreasonable to assume an offset of 50% of patients when

this is unlikely to occur in clinical practice. However, the PSCR applied a revised percentage of 50% to the financial estimates to ‘demonstrate the impact of this change’, although this was applied to the Option A financial model rather than the Option B financial model (no IO retreatment). The impact of increasing the offset to 50% for Option B is presented in Table 14.

- 4.34 The submission did not accept the advice of the PBAC to assume an uptake rate of 30–40% in the first 2 years of listing (para 5.10, nivolumab PSD, July 2023 PBAC meeting). The PBAC previously 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 previously considered the uptake of nivolumab may be lower than estimated (72.5% for eligible Stage IB, II and IIIA 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. The submission stated that ‘As the PBAC has previously considered the value of 72.5% as appropriate, it has again been applied in these financial estimates across both retreatment scenarios’. The PSCR reiterated that input from clinicians actively treating NSCLC in the Australian healthcare system represent the most robust source to estimate for neoNIVO+neoChemo uptake (72.5%). However, in response to the PBAC’s advice from the July meeting that uptake should be reduced in Year 1 and Year 2, the PSCR revised the uptake to 35% in the updated financial estimates. In making this amendment the estimated proportion of patients currently treated with atezolizumab and durvalumab that would instead be treated with neoNIVO+neoChemo was also reduced in proportion to the reduction in uptake for neoNIVO+neoChemo. This was considered to be appropriate.
- 4.35 Table 9 provides a summary of the estimates of patient numbers and prescriptions and financial impact across the 3 submissions.

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Table 9: Estimation of number of treated patients and prescriptions and financial impact for the March 2024, July 2023 and March 2023 submissions.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use by patient population, July 2023 and March 2024 PSCR: shaded rows are the same (uptake of 35% in years 1 and 2)</b>						
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
<b>Estimated extent of use, March 2024 PSCR (uptake of 35% in years 1 and 2)</b>						
Total number of incident patients treated for both Option A and Option B	2	2	2	2	2	2
Number of scripts dispensed for both Option A and Option B	2	2	2	2	2	2
<b>Estimated financial implications of nivolumab – March 2024 PSCR – effective price (uptake of 35% in years 1 and 2; AEMP corrected for Option B)</b>						
Option A (\$)	3	3	4	4	4	4
Option B (\$)	3	3	4	5	5	5
<b>Estimated extent of use, July 2023 re submission</b>						
Total number of patients treated <sup>a</sup>	2	2	2	2	2	2
Number of scripts dispensed	2	2	2	2	2	2
<b>Estimated financial implications of nivolumab – July 2023</b>						
Total cost to the PBS/RPBS, including patient copayments(\$)	4	4	4	4	4	4
<b>Estimated extent of use March 2023 submission</b>						
Number of patients treated	2	2	2	2	2	2
Number of scripts dispensed	2	2	2	2	2	2
<b>Estimated financial implications of nivolumab March 2023 submission</b>						
Total cost to the PBS/RPBS, including patient copayments	5	5	5	5	5	5

Source: PSCR attached workbooks. Table 4, nivolumab PSD, July 2023 PBAC Meeting.

AEMP = approved ex-manufacturer price

<sup>a</sup> 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)

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$10 million to < \$20 million

<sup>4</sup> \$20 million to < \$30 million

<sup>5</sup> \$30 million to < \$40 million

4.36 The estimated financial implications for reduced use of immunotherapies in other settings over the 3 submissions are presented separately in Table 10 and Table 11. The ESC noted these estimates use the published prices for atezolizumab and durvalumab and hence overestimate the offsets.

**Table 10: Estimated financial implications for reduced use of immunotherapies in other settings, March 2024 PSCR (uptake 35% in years 1 and 2) and 21% IO offset for Option A, 29% IO offset for Option B**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Atezolizumab (Options A and B)</b>						
Number of patients	1	1	1	1	1	1
Number of scripts	2	2	2	2	2	2
Net cost PBS/RPBS	3	3	3	3	3	3
<b>Durvalumab (Options A and B)</b>						
Number of patients	1	1	1	1	1	1
Number of scripts	1	1	1	1	2	2
Net cost PBS/RPBS	3	3	3	3	3	3
<b>Pembrolizumab (Option A)</b>						
Number of patients	1 <sup>2</sup>	1	1	1	1	1
Number of scripts	2	2	2	2	2	2
Net cost PBS/RPBS	3	3	3	3	3	3
<b>Pembrolizumab (Option B)</b>						
Number of patients	1	1	1	1	1	1
Number of scripts	2	2	2	2	2	2
Net cost PBS/RPBS	3	3	3	3	3	3
<b>Total cost to the PBS/RPBS including patient copayments (Option A)</b>	3	3	3	3	3	3
<b>Total cost to the PBS/RPBS including patient copayments (Option B)</b>	3	3	3	3	3	3

Source: PSCR attached workbooks.

IO = immunotherapy

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> net cost saving

**Table 11: Estimated financial implications for reduced use of immunotherapies in other settings, July 2023 submission**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Atezolizumab<sup>a</sup></b>						
Number of patients	1	1	1	1	1	1
Number of scripts	1	1	1	1	1	1
Net cost	3	3	3	3	3	3
<b>Durvalumab<sup>b</sup></b>						
Number of patients	1	1	1	1	1	1
Number of scripts	1	1	1	1	2	2
Net cost	3	3	3	3	3	3
<b>Pembrolizumab<sup>c</sup></b>						
Number of patients	1	1	1	1	1	1
Number of scripts	2	2	2	2	2	2
Net cost	3	3	3	3	3	3
<b>Total cost to the PBS/RPBS, including patient copayments</b>	3	3	3	3	3	3

Source: Table 4, nivolumab PSD, July 2023 PBAC Meeting

<sup>a</sup> Adjuvant Stage II-IIIa, PD-L1 >50% NSCLC

<sup>b</sup> Unresectable Stage III NSCLC

<sup>c</sup> Pembrolizumab as a proxy for all metastatic PD-(L)1 treatment options.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> net cost saving

4.37 The estimated net costs for Option A to the PBS/RPBS are shown in Table 12. These estimates assume 35% uptake of neoadjuvant nivolumab in years 1 and 2 and cost offsets in 21% of patients. The offsets are based on the published prices for atezolizumab and durvalumab and known effective price for pembrolizumab.

**Table 12: Estimate of net overall financial impact to the PBS/RPBS, Option A. PSCR (uptake 35% in years 1 and 2, 21% offset)**

	2024	2025	2026	2027	2028	2029
Cost to PBS/RPBS (neoNIVO)	1	1	2	2	2	2
Cost offset to PBS/RPBS (reduced immunotherapy use in other contexts)	3	3	3	3	3	3
<b>Net cost to PBS/RPBS</b>	4	4	4	4	4	4

Source: PSCR, attached workbook for Option A.

Abbreviations: neoNIVO = neoadjuvant nivolumab; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

<sup>1</sup> \$10 million to < \$20 million

<sup>2</sup> \$20 million to < \$30 million

<sup>3</sup> net cost saving

<sup>4</sup> \$0 to < \$10 million

4.38 The estimated net costs for Option B to the PBS/RPBS are shown in Table 13. These estimates assume 35% uptake of neoadjuvant nivolumab in Years 1 and 2 and cost offsets in 29% of patients. The offsets are based on the published prices for atezolizumab and durvalumab, and the known effective price for pembrolizumab.

**Table 13: Estimate of net overall financial impact to the PBS/RPBS, Option B. PSCR (uptake 35% in years 1 and 2, correct AEMP, 29% offset),**

	2024	2025	2026	2027	2028	2029
Cost to PBS/RPBS (neoNIVO)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost offset to PBS/RPBS (reduced immunotherapy use in other contexts)	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Net cost to PBS/RPBS</b>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>

Source: PSCR, attached workbook for Option B.

Abbreviations: neoNIVO = neoadjuvant nivolumab; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

<sup>1</sup> \$10 million to < \$20 million

<sup>2</sup> \$20 million to < \$30 million

<sup>3</sup> \$30 million to < \$40 million

<sup>4</sup> net cost saving

<sup>5</sup> \$0 to < \$10 million

4.39 The total cost to the PBS/RPBS of listing nivolumab according to Option A was estimated to be \$20 million to < \$30 million in Year 6, and a total of \$100 million to < \$200 million in the first 6 years of listing. For Option B, the estimated costs were \$30 million to < \$40 million in year 6 and \$100 million to < \$200 million over 6 years.

4.40 The impact of using the PBAC recommended offset for reduced immunotherapy use in other contexts (50%) for Option B is shown below. The offsets are based on the published prices for atezolizumab and durvalumab, and the known effective price for pembrolizumab.

**Table 14: Estimate of net overall financial impact to the PBS/RPBS, Option B (uptake 35% in years 1 and 2, correct AEMP, 50% offset)**

	2024	2025	2026	2027	2028	2029
Cost to PBS/RPBS (neoNIVO)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost offset to PBS/RPBS (reduced immunotherapy use in other contexts)	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Net cost to PBS/RPBS</b>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>

Source: Constructed using the PSCR attached workbook for Option B.

Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

<sup>1</sup> \$10 million to < \$20 million

<sup>2</sup> \$20 million to < \$30 million

<sup>3</sup> \$30 million to < \$40 million

<sup>4</sup> net cost saving

## Financial Management – Risk Sharing Arrangements

4.41 The submission stated:

‘The application of a reduced effective price and incorporation of cost-offsets from reduced use of immunotherapy in other settings results in a modest overall net cost to the PBS/RPBS. The modest overall net cost was calculated using the published price of atezolizumab and durvalumab and the known effective price of pembrolizumab. As

such, the Sponsor acknowledges that the estimated overall net cost will be greater than the estimate presented in Table 10, however likely to remain <|% of the current NSCLC cap value.

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, it is 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 (applied above) and effective prices for adjuvant atezolizumab, durvalumab and metastatic pembrolizumab.'

## 5 PBAC Outcome

- 5.1 At its July 2023 meeting, the PBAC recommended the listing of nivolumab (Opdivo®) for the neoadjuvant treatment of surgically-resectable non-small cell lung cancer (NSCLC). At the March 2024 meeting, the PBAC did not recommend any revisions to its previous advice. Specifically, the PBAC did not recommend retreatment with immunotherapy (IO) in those who relapse with metastatic disease (presented as Option A in the submission) as there was insufficient evidence to support the effectiveness of IO retreatment following use in surgically-resectable NSCLC, and this resulted in it being unknown if retreatment was cost-effective. The PBAC advised further discussions were required with relevant stakeholders regarding retreatment across cancer listings more generally. The PBAC also did not recommend a price increase for nivolumab for the scenario of no IO retreatment (presented as Option B in the submission). The PBAC noted the economic model was sensitive to the inputs regarding treatment in the metastatic setting and considered it was unlikely that neoadjuvant nivolumab was cost-effective with the proposed |% increase in price.
- 5.2 The primary reason for this outcome was due to the comparative clinical evidence presented.
- 5.3 The PBAC noted that the submission requested modification to the listing for nivolumab recommended in July 2023: Option A allowing IO retreatment; Option B not permitting IO retreatment. The PBAC noted for Option A the Pre-PBAC Response proposed flow-on changes to IO listings in the metastatic setting restricting retreatment to patients who had not experienced disease progression while receiving or within 6 months of receiving neoadjuvant treatment. The PBAC noted Option B proposed a PBS restriction aligned with previous PBAC advice but increased the ex-manufacturer price from \$| per 100 mg to \$| per 100 mg.

### Option A: Allowing IO retreatment

- 5.4 The PBAC noted comments from health care professionals and organisations expressing support for IO retreatment following use in surgically-resectable NSCLC for those who relapse with metastatic disease. The PBAC noted input from Lung Foundation Australia supporting a nivolumab listing that allows IO retreatment and

the Medical Oncology Group of Australia's (MOGA) strong support for the submission.

- 5.5 The PBAC recalled that it previously considered in March 2023 that subsequent use of immunotherapy may be clinically appropriate in those who relapse with metastatic disease, but expressed a preference for evidence to support such use (para 7.5, nivolumab PSD, March 2023 PBAC meeting). In July 2023, due to a lack of clinical evidence repeat use of immunotherapy in NSCLC patients who relapse with metastatic disease could not be supported by the Committee. The PBAC also recalled it previously noted that it would reconsider the recommendation to exclude retreatment in metastatic disease should evidence supporting such use become available (para 5.3, nivolumab PSD, July 2023 PBAC meeting).
- 5.6 The PBAC noted the primary evidence for IO retreatment in the submission was based on 18 studies, including 11 retrospective case series, 1 single arm clinical trial and 5 systematic reviews and/or meta-analyses. The PBAC noted the evidence presented in the submission to support IO retreatment did not include patients receiving neoadjuvant treatment for resectable disease and did not report an estimate for the magnitude of benefit associated with IO retreatment. Overall, the PBAC considered, although there may be a clinical rationale for IO retreatment in the absence of progression while on neoNIVO or within 6 months of receiving neoNIVO, that without an estimate of the magnitude of benefit for IO retreatment it was unknown if retreatment was cost-effective.
- 5.7 The PBAC recalled in March 2023 that it considered it would be appropriate to manage the uncertainties associated with retreatment with IO in metastatic disease within the risk-sharing agreement (RSA), given there is no clinical data to support such use (para 7.20, nivolumab PSD, March 2023 PBAC meeting). The PBAC noted the submission proposed an increase to the RSA financial caps to account for retreatment which did not address the uncertain cost-effectiveness of such use.
- 5.8 The PBAC advised further discussions were required with relevant stakeholders regarding retreatment across cancer listings more generally.

Option B: Not permitting IO retreatment

- 5.9 The PBAC recalled it had previously considered nivolumab to be acceptably cost-effective based on the economic model included in the July 2023 resubmission and a re-specified base case that resulted in an ICER of \$25,000 to < \$35,000 per QALY gained (para 5.7, nivolumab PSD, July 2023 PBAC Meeting). The PBAC noted that the current submission stated that while IO retreatment was not supported in July 2023, the accepted economic model included IO retreatment and therefore the economic model for Option B in the current submission was amended to remove IO retreatment for those who relapse with metastatic disease. Removal of IO retreatment decreased the quality adjusted life years (QALYs) and costs for the neoadjuvant nivolumab arm and hence reduced both the incremental QALYs and costs. The PBAC noted that the incremental QALYs gained reduced from 0.66 to 0.51 (23% reduction) but there was a larger impact on the incremental costs which were reduced from \$1 to \$0.5 (50%), and

hence the ICER reduced from \$25,000 to < \$35,000 to \$15,000 to < \$25,000 per QALY gained. The PBAC further noted that the submission stated that if IO retreatment is precluded from the economic model, the unit price for nivolumab should be increased to maintain an ICER of \$25,000 to < \$35,000 per QALY gained.

- 5.10 The PBAC noted that uncertainties with the economic model related to the clinical and modelled benefits associated with IO retreatment had not been addressed in the submission and reiterated its previous advice that the one-off costs and health outcomes associated with metastatic treatment options applied on transition to the distant metastasis (DM) health state and their application in the model were not appropriate. For this reason, the PBAC advised that it was not appropriate to determine an increase in price for nivolumab based on the modelled reduction in incremental costs and health outcomes associated with the removal of IO retreatment in the economic model. The PBAC also noted that the Option B economic model was sensitive to changes to the assumptions associated with the one-off costs and health benefits of IO treatment in the metastatic state and that plausible changes in either the assumed costs or benefits resulted in ICERs of approximately \$45,000 to < \$55,000 per QALY gained. Overall, the PBAC considered it was unlikely that neoadjuvant nivolumab was cost-effective with the proposed  $\frac{1}{2}$ % increase in price.

#### Options A and B

- 5.11 The PBAC noted the submission had provided revised financial estimates that removed duplicated atezolizumab and durvalumab patients. The PBAC also noted that the Pre-Sub Committee Response (PSCR) provided further updates to the financial estimates that incorporated an uptake of 35% per annum in the first two years of listing and increased the cost-offset percentage associated with the reduced use of IO in the metastatic setting to 50% (noting that the increased percentage should be applied to the Option B financial model). The PBAC considered that these amendments were appropriate and aligned with previous advice (para 5.11, nivolumab PSD, July 2023 PBAC Meeting).
- 5.12 The PBAC noted that this submission is eligible for an Independent Review.

#### **Outcome:**

Not recommended

## **6 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.

## **7 Sponsor's Comment**

The Sponsor would like to reiterate its commitment to finding a pathway forward for immuno-oncology retreatment across early and advanced disease, as evidenced by this submission and a previous submission provided for melanoma which was recommended (Item 6.09, Nov 2022 PBAC Meeting). BMS Australia are looking forward to working with the PBAC to achieve this important change in treatment paradigm for cancer patients.