

6.06 NIVOLUMAB,

Injection concentrate for I.V. infusion 40 mg in 4 mL

Injection concentrate for I.V. infusion 100 mg in 10 mL

Opdivo[®],

Bristol-Myers Squibb Australia Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested 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 Listing was requested on the basis of a cost-utility analysis versus neoadjuvant chemotherapy (neoChemo). Other nominated comparators were adjuvant chemotherapy (adjChemo) and adjuvant chemotherapy followed by atezolizumab (adjChemo+adjATEZO). Only the comparison with neoChemo was captured in the economic analysis and financial estimates.
- 1.3 A summary of the key components of the clinical issue addressed by the submission 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 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 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.

^aThe 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.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. The TGA application was submitted as part of Project Orbis, an initiative of the Food and Drug Administration (FDA) for international collaboration among regulatory agencies to review new cancer treatments. At the time of PBAC consideration the Delegate’s Overview was available. The pre-PBAC response stated that nivolumab was TGA registered on the 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 Table 2 summarises the international regulatory approval status for neoadjuvant treatment with nivolumab in resectable NSCLC at the time of the evaluation.

Table 2: Summary of international regulatory approval status for nivolumab as a neoadjuvant treatment for resectable non-small cell lung cancer (NSCLC)

Agency	Approved/requested indication	Approval date	Registration conditions	Assessment report
Food and Drug Administration (FDA)	Nivolumab in combination with platinum-doublet chemotherapy is indicated as neoadjuvant treatment of adult patients with resectable (tumours \geq 4 cm or node positive) non-small cell cancer (NSCLC).	4 th March 2022	None	Not available
European Medicines Association (EMA)	Pending (EMA submission accepted 29 th March 2022). The specific indication being sought was not provided.	Under evaluation	Pending	Pending
Health Canada	Nivolumab in combination with platinum-doublet chemotherapy is indicated as neoadjuvant treatment of adult patients with resectable (tumours \geq 4 cm or node positive) NSCLC.	17 th August 2022	None	Not available
Medicines and Healthcare products Regulatory Agency (MHRA) (United Kingdom)	OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable (tumours \geq 4 cm or node positive) non-small cell lung cancer in adults.	16 th August 2022	None	Not available

Source: Table 12, pp35-36 of the submission

Previous PBAC consideration

- 2.4 The PBAC has not previously considered nivolumab in combination with platinum-doublet chemotherapy (neoNIVO+neoChemo) as a neoadjuvant treatment for resectable NSCLC.
- 2.5 At the July 2022 meeting, the PBAC recommended listing atezolizumab, another programmed cell death ligand-1 (PD-L1) inhibitor, for the adjuvant treatment of patients with Stage II to IIIA NSCLC whose tumours have PD-L1 expression on $\geq 50\%$ of tumour cells and following a complete resection and no progression after platinum-based adjuvant chemotherapy. Listing was effective from 1 November 2022.
- 2.6 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.

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

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Proposed restriction: Scenario 1:

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals				
MEDICINAL PRODUCT Form	Dispensed Price Max Amt	PBS item code	Maximum amount	No. of Repeats
NIVOLUMAB Injection	<u>Published price</u> \$7,189.57 (public) ^a \$7,330.64 (private) ^a <u>Effective price</u> \$ (public) ^b \$ (private)	New (Public) New (Private)	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)				
Episodicity: [blank]				
Severity: [blank]				
Condition: Non-small cell lung cancer				
Indication: Non-small cell lung cancer Resectable (tumours ≥ 4 cm or node positive) non-small cell lung cancer (NSCLC)				
Treatment Phase: [blank]				
Clinical criteria:				
<i>The condition must be at least one of: (i) node positive, (ii) at least 4 cm in size</i>				
AND				

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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>
<i>Patient must have an Eastern Cooperative Performance Group (ECOG) performance status of 0 or 1,</i>
AND
Clinical criteria:
<i>The treatment must be in combination with platinum-based chemotherapy</i>
AND
<i>The treatment must not exceed a total of 3 doses of nivolumab</i>
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

Proposed restriction Scenario 2:

Restriction Summary / Treatment of Concept: [New 1] : Authority Required (STREAMLINED)
Indication: Non-small cell lung cancer Resectable (tumours \geq 4 cm or node positive) non-small cell lung cancer (NSCLC)
Treatment Phase: [blank]
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>
<i>Patient must have an Eastern Cooperative Performance Group (ECOG) performance status of 0 or 1,</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>
<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
<i>The treatment must not exceed a total of 3 doses of nivolumab</i>
Prescribing instructions:
<i>Where treatment is for non-squamous type disease, 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>
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

^aThe published dispensed prices as presented in Section 1 of the submission were different from the published dispensed prices calculated in the financial analysis (\$7,197.37 [public]; \$7,330.61 [private]). The prepared dispensing fee (\$7.82) should be removed from the dispensed

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price for nivolumab in a public hospital setting to be in line with the Efficient Funding of Chemotherapy (EFC) Program. The revised published dispensed prices for a maximum amount (360 mg), as calculated in the financial analysis (with the removal of the dispensing fee for the public hospital setting) is \$7,189.55 (public hospital) and \$7,330.61 (private hospital).

^bThe effective dispensed price in a public hospital setting as calculated in the submission includes the prepared dispensing fee (\$7.82). This is not in line with the EFC Program. After removing this fee, the revised effective dispensed price in a public hospital is \$[REDACTED] for a maximum amount of 360 mg.

- 3.2 The submission proposed a special pricing arrangement (SPA) with an effective public hospital DPMA of \$[REDACTED] (published \$7,189.57) and an effective private hospital DPMA of \$[REDACTED] (published \$7,330.64). The proposed published dispensed price for maximum amount (DPMA) was consistent with the published price of nivolumab for other PBS listed indications. The effective dispensed price in a public hospital as calculated in the submission includes the prepared dispensing fee (\$7.82). This is not in line with the Efficient Funding of Chemotherapy (EFC) Program.
- 3.3 The submission noted that the proposed published price for nivolumab was lower than the effective price. The submission stated that the proposed effective price was based on the cost-effectiveness analysis presented in the submission and claimed it was reflective of the value offered by nivolumab in the proposed use. The submission stated that if the PBAC recommend nivolumab for the proposed indication, the sponsor is willing to work with the Department to appropriately implement the necessary pricing arrangements to ensure the timely listing of (and access to) nivolumab.
- 3.4 The submission proposed two PBS listing scenarios. Scenario 1 (preferred by the sponsor) was a listing that is agnostic to epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) status, and is consistent with the proposed TGA indication. Scenario 2 was a listing mirroring the eligibility criteria of the key CM816 trial which excluded patients with known sensitising EGFR mutations or ALK alterations.
- 3.5 The justification provided in the submission for Scenario 1 was that patients with resectable NSCLC, who have evidence of sensitising EGFR mutations or ALK alterations, are unable to access EGFR or ALK inhibitors through the PBS. These agents are currently PBS listed only for advanced (locally advanced and metastatic [Stage IV]) disease. EGFR or ALK driver mutations have consistently shown poor response to immunotherapy. Consequently, these patients are usually excluded from trials investigating immunotherapy in lung cancer. There is consensus in the literature that upfront treatment of tumours with activating EGFR or ALK alterations with immune

checkpoint inhibitors (ICIs) should be avoided^{1,2,3}. The Pre-Sub-Committee Response (PSCR) reiterated the justifications provided in the submission, however stated the sponsor was willing to accept Scenario 2. The ESC considered that there was inadequate evidence provided in the submission to support Scenario 1 and supported the use of Scenario 2 for the restriction criteria.

- 3.6 The dose regimen of nivolumab in the key CM816 trial was 360 mg every three weeks (Q3W) for a maximum of 3 cycles which was consistent with the recommended dose regimen in the PI.
- 3.7 The evaluation considered the proposal to not have PBS restrictions by phase (Initial and Continuing) appeared appropriate as there are no specific response criteria required for continuing nivolumab therapy in the neoadjuvant setting.
- 3.8 The two scenario populations proposed in the submission are unselected in terms of PD-L1 status. The evaluation questioned whether nivolumab should be restricted to patients who express PD-L1 and/or have high expression of PD-L1. Pre-specified subgroup analyses in CM816 showed that the event free survival (EFS) benefit associated with neoNIVO+neoChemo versus neoChemo, in the intention to treat (ITT) population, may have been driven by the observed benefit in patients whose tumours expressed PD-L1, particularly for the high PD-L1 expression subgroup (PD-L1 < 1%: hazard ratio [HR] = 0.85 [95% CI: 0.54, 1.32]; PD-L1 ≥ 1%: HR = 0.41 [95% CI: 0.24, 0.70]; PD-L1 1-49%: HR = 0.58 [95% CI: 0.30, 1.12]; and PD-L1 ≥ 50%: HR = 0.24 [95% CI: 0.10, 0.61]). This trend in predictive effect was similarly observed with the adjuvant use of atezolizumab in the IMpower010 trial. The PSCR did not support restricting nivolumab to patients who express PD-L1 and/or have high expression of PD-L1. The ESC noted that PD-L1 expression appeared to be a driver of benefit (see paragraph 6.27) but considered that restricting access based on PD-L1 status may not be appropriate. The ESC noted the concerns raised by MSAC regarding the use of PD-L1 immunohistochemistry testing to determine eligibility for treatment with PD-L1 checkpoint inhibitors in their September 2022 position statement⁴.
- 3.9 The evaluation questioned whether the restriction should specify the stage of disease as in the key CM816 trial (resectable Stage IB, Stage II or Stage IIIA) and considered

¹ Faltermeier CM, Lee JM. Neoadjuvant immunotherapy in resectable non-small cell lung cancer at a checkpoint. *Translational Lung Cancer Research*. 2021;10(12):4328

² Hellmann MD, Chaft JE, William Jr WN, Rusch V, Pisters KM, Kalhor N, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. *The lancet oncology*. 2014;15(1):e42-e50.

³ Kwiatkowski DJ, Rusch VW, Chaft JE, Johnson BE, Nicholas A, Wistuba II, et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3). *American Society of Clinical Oncology*; 2019

⁴ Medical Services Advisory Committee. (2022) MSAC Position Statement on programmed death-ligand 1 (PD-L1) immunohistochemistry testing to determine eligibility for treatment with PD-(L)1 checkpoint inhibitors. MSAC Position Statement - PD-L1 testing - Ratified -26Sept - clean.pdf

stating the condition as 'Resectable (Tumours \geq 4 cm or node positive) non-small cell lung cancer (NSCLC)' in the proposed restriction appears too broad.

- 3.10 A tumour may be considered technically resectable, yet the patient may not be fit for surgery due to other clinical considerations, such as the extent of lymph node involvement and high surgical risk in a compromised patient⁵. Thus, the evaluation considered there is a risk that patients may be offered neoNIVO+neoChemo whilst unfit for surgery.
- 3.11 Current PBS restrictions for nivolumab, pembrolizumab, and atezolizumab for the treatment of metastatic NSCLC disease specify that the patient must not have received prior treatment with a PD-L1 inhibitor for NSCLC. The submission 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. The submission's rationale was based on i) evidence from CM816 would not be forthcoming in the near future given the high proportion of patients who are recurrence/metastasis free, ii) clinical advice received by the sponsor is that PD-L1 inhibitors remain highly effective in metastatic disease, iii) exposure to neoadjuvant nivolumab is only a maximum of 3 doses, and iv) the biological plausibility assumption that tumours responding to nivolumab prior to surgical resection would remain sensitive to PD-L1 inhibitor therapy after disease recurrence/metastasis. Recognising that there is a clinical rationale for the retreatment with ICIs, if these agents are used earlier in treatment, there is paucity of clinical and economic evidence available to support retreatment. The ESC considered that there is currently insufficient evidence to support retreatment with PD-L1 inhibitors in metastatic disease, however noted that without the requested flow on amendments patients would not be able to access immunotherapies for metastatic disease, despite having only received a short course of neoadjuvant nivolumab. The pre-PBAC response highlighted that only 0.6% of patients treated with neoNIVO discontinued treatment due to disease progression/recurrence in CM816 and argued that the low rate of resistance following up to 3 doses of nivolumab is indicative of a situation whereby tumours would remain responsive to further PD-L1 treatment upon progression/recurrence to Stage IV (metastatic) disease. The pre-PBAC response noted that the proposed flow on amendments to the PBS restrictions for nivolumab, pembrolizumab, and atezolizumab for patients with Stage IV (metastatic) NSCLC would allow patients treated with neoNIVO access to PD-L1 treatment upon disease progression/recurrence.
- 3.12 Flow on effects to the Medicare Benefits Schedule (MBS): The submission noted that if the PBAC recommended the PBS listing under Scenario 2 (i.e., excluding EGFR mutations/ALK alterations), implementing the PBAC recommendation would be dependent on the Medical Services Advisory Committee (MSAC) supporting a change

⁵ Shamji FM, Beauchamp G. Assessment of Operability and Resectability in Lung Cancer. *Thoracic Surgery Clinics*. 2021;31(4):379-91.

to the MBS item for EGFR testing of tumour tissue (Item 73337). The submission noted that a streamlined co-dependent submission requesting an amendment to MBS Item 73337, allowing EGFR testing through the MBS to determine eligibility to access nivolumab as a neoadjuvant treatment through the PBS, was submitted for consideration by MSAC.

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

4 Population and disease

- 4.1 Lung cancer is a common form of cancer in Australia with 14,529 incident cases reported in 2022⁶. In consideration of the high burden of disease and poor survival for patients with NSCLC, there is a need for effective treatment options which delay disease recurrence or progression, prolong survival and do not have a detrimental impact on patient quality of life (QoL). Results of a meta-analysis showed that the absolute survival improvement associated with pre-operative chemotherapy was only 5% (from 40% to 45%) at 5 years⁷.
- 4.2 Generally, patients with Stage I-IIIa NSCLC disease, if deemed operable, would be considered candidates for surgical resection of the primary tumour. Determination of tumour resectability involves consideration of a range of factors such as tumour size/location, pulmonary and cardiac function, and the patient's willingness to undergo surgery.
- 4.3 neoNIVO+neoChemo is proposed to be used as an alternative to adjChemo (secondary comparator) in patients with resectable NSCLC or as an alternative to adjChemo+adjATEZO (supplementary comparator) in a proportion of patients with Stage II-IIIa NSCLC with high PD-L1 expression ($\geq 50\%$), and who have undergone surgical resection. In this scenario, patients would first undergo surgical resection and receive adjChemo, with a subgroup (Stage II-IIIa, PD-L1 $\geq 50\%$) of patients going on to receive adjATEZO.
- 4.4 Nivolumab is a fully human immunoglobulin G4 monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor on T-cells. It acts as an immunomodulation agent by blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2.
- 4.5 The ESC noted recent MSAC support of the creation of a national lung cancer screening program, including a new Medicare item for low dose tomography scans for asymptomatic high-risk Australians to detect lung cancer earlier⁸. The ESC considered

⁶ AIHW (2022). Cancer Data in Australia. <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia>

⁷ Meta-analysis Collaborative Group. (2014). Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *The Lancet*, 383(9928), 1561–1571. [https://doi.org/10.1016/S0140-6736\(13\)62159-5](https://doi.org/10.1016/S0140-6736(13)62159-5)

⁸ Medical Services Advisory Committee. (2022) 1699 – National Lung Cancer Screening Program <http://msac.gov.au/internet/msac/publishing.nsf/content/1699-public>

the creation of such a program would make it likely that more patients would be identified who were suitable for neoadjuvant treatment.

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

5 Comparator

5.1 The nominated comparators and rationale provided in the submission are summarised in Table 3.

Table 3: Comparators nominated in the submission and rationale

Patient population	Comparator type	Comparator treatment	Rationale
Resectable (tumours ≥ 4 cm or node positive) NSCLC	Main	Neoadjuvant chemotherapy	The comparator treatment is currently available on the PBS and is likely to be replaced with the use of nivolumab plus chemotherapy if PBS listed as requested. Allows for the assessment of the incremental efficacy and safety of the addition of nivolumab to neoadjuvant use of chemotherapy.
Resectable (tumours ≥ 4 cm or node positive) NSCLC	Secondary	Adjuvant chemotherapy	The comparator treatment is currently available on the PBS and based on the CM816 trial results presented in the submission, it is likely that some clinicians would substitute adjuvant chemotherapy for neoadjuvant nivolumab plus chemotherapy.
Resected Stage II-III A NSCLC whose tumours have PD-L1 ≥ 50%	Supplementary	Adjuvant chemotherapy followed by atezolizumab	Atezolizumab was recommended to be listed on the PBS at the July 2022 PBAC meeting. It is likely that some clinicians would substitute adjuvant chemotherapy followed by atezolizumab for neoadjuvant nivolumab plus chemotherapy in the PBS-recommended population for atezolizumab, that is, resected Stage II-III A NSCLC whose tumours have PD-L1 ≥ 50%.

Source: Table 7, p28 of the submission.

NSCLC=non-small cell lung cancer; PD-L1=programmed cell death Ligand 1.

5.2 The evaluation considered the comparators nominated in the submission appear reasonable. However, in clinical practice, some patients, such as those with earlier stage NSCLC, may not be offered neoChemo before surgery, either because they are expected to have complete resection (R0 margins) or because this treatment approach is associated with modest survival benefit⁹ and the benefit-risk balance is unfavourable with neoChemo. With the availability of neoNIVO+neoChemo on the other hand, the benefit-risk balance may be considered favourable for some patients who would otherwise not be offered neoChemo alone. The ESC considered the nominated comparators reasonable. Further, the ESC considered that patients who

⁹ Meta-analysis Collaborative Group. (2014). Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *The Lancet*, 383(9928), 1561–1571. [https://doi.org/10.1016/S0140-6736\(13\)62159-5](https://doi.org/10.1016/S0140-6736(13)62159-5)

would not be offered neoChemo before surgery on clinical grounds would be unlikely to be offered neoNIVO+neoChemo instead.

- 5.3 The indirect comparisons between neoNIVO+neoChemo and adjChemo or adjChemo+adjATEZO were not considered in the economic analysis and financial estimates. The submission was based on the health outcomes and the costs of neoNIVO+neoChemo versus neoChemo in adult patients with resectable (tumours \geq 4 cm or node positive) NSCLC.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease and how the drug would be used in practice. The clinician considered that the 'once in a lifetime' ruling for immune therapy access on the PBS would need amendment if the use of checkpoint inhibitors as part of neoadjuvant treatment is recommended. The clinician argued that, due to the short course of immune therapy given as part of neoadjuvant treatment, the cancer would not develop resistance to checkpoint inhibition. The clinician stated it would be expected that the introduction of a treatment that was previously demonstrably active and effective when given over a short period of about two months, should be effective again when the patient receives the same treatment at a future date. The clinician also indicated that they expected patients that received neoadjuvant immune therapy would be precluded from receiving post operative adjuvant immune therapy, unless evidence emerges that demonstrates a clear clinical benefit.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from health care professionals described a range of benefits of treatment with nivolumab including the ability to reduce the risk of cancer recurrence and the relatively short duration of therapy required. The comments from Lung Foundation Australia and Rare Cancers Australia highlight the need for additional treatment options for this condition, due to the lack of access to targeted therapies and the resultant financial burden to individuals due to both the loss of earnings and the high out of pocket costs associated with treatment.
- 6.3 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 therapies¹⁰.

Clinical trials

- 6.4 The submission's primary evidence 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 (≥ 4 cm) – IIIA, American Joint Commission on Cancer (AJCC), 7th Edition)¹¹. The ITT population in CM816 consisted of 358 patients with most having Stage IIIA disease (64%). The requested population for the proposed neoNIVO+neoChemo listing was patients with resectable (tumours ≥ 4 cm or node positive) NSCLC regardless of PD-L1 expression status.
- 6.5 For the secondary comparator adjChemo, the submission's evidence was based on an adjusted/anchored indirect treatment comparison (ITC) (Bucher method¹²) between neoNIVO+neoChemo in CM816 with adjChemo in the NATCH trial, using neoChemo as the common reference arm. The 3-arm randomised controlled NATCH trial compared neoChemo (Q3W for 3 cycles) with surgery alone, and adjChemo (Q3W for 3 cycles) with surgery alone, in resectable NSCLC (Stage IA (≥ 2 cm), IB, II or T3N1, AJCC 6th Edition). Thus, the NATCH trial excluded patients with stage IIIA N2 disease. As the comparative effectiveness of the neoChemo and adjChemo arms of NATCH was not reported, this was derived in the submission using surgery alone as the reference arm.
- 6.6 For the supplementary comparator adjChemo+adjATEZO, the ITC was a modelled multi-step approach between neoNIVO+neoChemo in CM816 and adjChemo+adjATEZO in IMpower010 using NATCH to link the two studies. Stage-based criteria were assessed prior to surgery (clinical stage) in CM816, whereas pathological staging was used in IMpower010. The submission noted that the Bucher approach and other conventional ITC methods could not be used to conduct the ITC because of differences in the patient populations enrolled in the CM816 and IMpower010 trials. The ITC was also based on a subgroup of patients from the CM816 and IMpower010 trials whose tumours express PD-L1 $\geq 50\%$, given the positive PBAC recommendation for the adjuvant use of atezolizumab in this population. The linking trial, NATCH, was conducted over two decades ago (IMpower010 and CM816 were both conducted

¹⁰ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

¹¹ The CM816 trial initially had a treatment arm (Arm A) nivolumab plus ipilimumab. However, based on external data from a neoadjuvant trial (NADIM) which indicated that anti-PD-1+chemotherapy was associated with clinical benefit, Arm A was stopped and it was decided that randomisation will continue for the neoNIVO+neoChemo and neoChemo arms until a total of 350 patients were enrolled (protocol was revised in September 2018; Amendment No: 07, CM816 Revised Protocol 03).

¹² Bucher HC, Guyatt GH, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology*. 1997;50(6):683-91.

within the past 5 years), and thus PD-L1 status was not assessed as part of the study protocol.

6.7 Details of the CM816, NATCH, and IMpower010 trials are provided in Table 4.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct comparison between neoNIVO+neoChemo and neoChemo		
CM816 NCT0998528	<p>Randomized, open-label, Phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early stage NSCLC: Forde, P. M. et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer.</p> <p>Forde, P. M. et al. Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIa) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial.</p> <p>Spicer, J. et al. Surgical outcomes from the phase 3 CheckMate 816 trial: nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC).</p> <p>Girard, N. et al. Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment for resectable (IB-IIIa) non-small cell lung cancer (NSCLC): Event-free survival (EFS) results from the phase 3 CheckMate 816 trial.</p>	<p>16 December 2021</p> <p><i>New England Journal of Medicine</i> 2022; 386 (21), 1973-1985.</p> <p><i>Cancer research</i> 2021; 81, (S13): Abstract CT003.</p> <p><i>Journal of clinical oncology</i> 2021; 39, (15), 8503.</p> <p><i>Cancer Research</i> 2021; <i>American Association for Cancer Research Annual Meeting (ACCR, 82)</i>.</p>
Trials used for indirect comparisons with neoNIVO+neoChemo from CM816		
NATCH NCT00913705	Felip, E. et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer.	<i>Journal of clinical oncology</i> 2010; 28(19), 3138-3145
IMpower010 NCT02486718	<p>Felip, E. et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIa non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial.</p> <p>Kenmotsu, H. et al. Adjuvant atezolizumab in Japanese patients with resected stage IB-IIIa non-small cell lung cancer (IMpower010).</p> <p>Altorki, N. et al. PL02.05 IMpower010: Characterization of Stage IB-IIIa NSCLC Patients by Type and Extent of Therapy Prior to Adjuvant Atezolizumab.</p> <p>Wakelee, H. A. et al. IMpower010: primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIa non-small cell lung cancer (NSCLC).</p>	<p><i>The Lancet</i> 2021; 398(10308), 1344-1357</p> <p><i>Cancer Science</i> 2022; September 5. doi: 10.1111/cas.15564.</p> <p><i>Journal of Thoracic Oncology</i> 2021; 16 (10 Supplement), S845-S846.</p> <p><i>Journal of clinical oncology</i>; 2021; (39), S15, 8500.</p>

Source: Table 19, pp53-4 of the submission.

6.8 The key features of the included trials are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	NSCLC patient population	Outcomes	Use in modelled evaluation
CM816	358	neoNIVO+neoChemo vs. neoChemo (3 cycles) R, OL. Median follow-up 29.5 months (October 2021 data cutoff)	Low	ITT: neoadjuvant setting Resectable. Clinical Stage 1B-IIIa (AJCC 7 th Edition). Stage 1B-II: 35% Stage IIIa: 64%	pCR, MPR, EFS, TTDM, OS, AEs.	TTLR ^a Time to any progression ^a , Survival in event-free patients ^a Post-LR survival ^a
NATCH	624	R, 3-arm: neoChemo (3 cycles)+surgery, surgery alone, Surgery+adjChemo (3 cycles).	Indirect comparison with CM816: High	ITT: Clinical stage IA, tumour size > 2 cm, IB, II, or T3N1 NSCLC (AJCC 6 th Edition). Stage 1: 73-78% Stage II – T3N1: 22-27%	DFS	Indirect comparison not captured in economic analysis
IMpower010	1005	ATEZO vs. BSC R, OL Median follow-up for OS ~32 months (January 2021 data cutoff)	Indirect comparison with CM816: High	ITT: Adjuvant setting Completely resected and following adjChemo. Pathological Stage IB-IIIa (AJCC 7 th Edition) Stage 1B: 13% Stage II: 47% Stage IIIa: 40%	DFS, OS, Safety	Indirect comparison not captured in economic analysis

Source: Sections 2.3 and 2.4 of the submission, the CM816 Clinical Study Report, and corresponding publications for NATCH (Felip 2010) and IMpower010 (Felip 2021).

Adj=adjuvant; AEs=adverse events; AJCC=American Joint Committee on Cancer; ATEZO=atezolizumab; BSC=best supportive care; chemo=chemotherapy; DB=double blind; DFS=disease free survival; EFS=event free survival; IC=immune cell; ITT=intention to treat; LR = locoregional recurrence; MC=multi-centre; MPR=major pathological response; neo=neoadjuvant; NSCLC=non-small cell lung cancer; OL=open label; OS=overall survival; pCR=pathological complete response; PD-L1=programmed cell death Ligand 1; R=randomisation; TC = tumour cell; TTLR=time to locoregional recurrence; TTMD=time to metastatic disease

Note: CM816 - Stratified by PD-L1 expression status (< 1% vs ≥ 1% or not evaluable), disease stage (IB/II vs IIIa), and gender. NATCH - Stratified by tumour size (< 3 vs. 3 to 5 vs. > 5 cm) and age (≤ 60 years vs. > 60 years). IMpower010 - Stratified by gender, tumour histology (squamous vs. non-squamous), extent of disease (stage IB vs. stage II vs. stage IIIa), and PD-L1 tumour expression status (TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1).

^a The economic model used trial data on TTLR, time to any disease progression, survival in event-free patients and post-LR survival. These were not outcomes pre-specified in the CM816 study protocol.

6.9 The risk of bias was considered low for the direct comparison in the CM816 trial and high for the indirect comparisons between the CM816, NATCH, and IMpower010 trials.

Comparative effectiveness

- 6.10 In the CM816 trial, effectiveness data were based on two data cutoff dates:
- Final analysis of co-primary endpoint of pathological complete response (pCR) rate¹³: data cutoff 16 September 2020; and
 - Interim analysis 1 of EFS¹⁴ and OS: data cutoff 20 October 2021.
- 6.11 The submission noted that no claim was being made on the basis of pCR as a surrogate for overall survival (OS) as follow-up for OS in CM816 is ongoing.
- 6.12 The EFS results are summarised in Table 6. The EFS Kaplan-Meier (KM) curves are presented in Figure 1.

Table 6: Duration of event-free survival - CM816: BICR

	neoNIVO+neoChemo	neoChemo	Difference	HR neoNIVO+neoChemo vs. neoChemo (95% CI)
Interim analysis 1: median follow-up 29.5 months				
n/N with event (%)	64/179 (35.8)	87/179 (48.6)		0.63 (0.45, 0.87) p-value=0.0052 ^a
Median time-to-event, months, (95% CI)	31.6 (30.2, NA)	20.8 (14.0, 26.7)	10.8	
EFS rate at 12 months, (95% CI)	76.1% (68.8%, 81.9%)	63.4% (55.3%, 70.4%)	12.7%	
EFS rate at 24 months, (95%CI)	63.8% (55.7%, 70.9%)	45.3% (37.0%, 53.2%)	18.5%	

Source: Table 46 and Table 48, p79 and p80 of the submission, and Table 7.1-1, p110 of the CM816 CSR

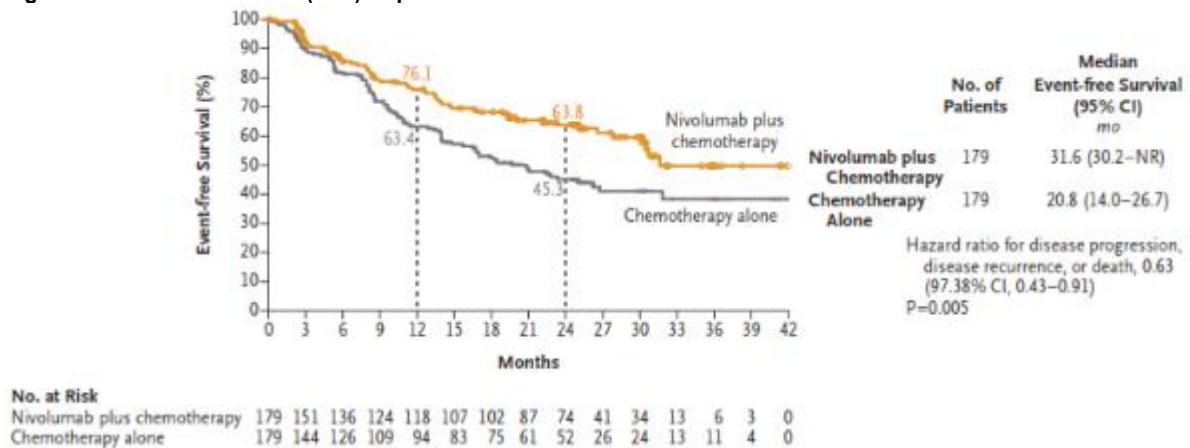
BICR=Blinded independent central review; Chemo=chemotherapy; CI=confidence interval; EFS=event free survival; HR = hazard ratio; NA=not available/not reached; NIVO=nivolumab.

^a Stratified log-rank test p-value. The p-value threshold for statistical significance at Interim analysis 1 was 0.0262.

¹³ pCR rate defined as the number of randomised subjects with an absence of residual tumour in lung resected tissue and lymph nodes per blinded independent pathological review (BIPR), divided by the number of randomised patients for each treatment arm.

¹⁴ EFS by blinded independent central review (BICR) was a composite endpoint defined as time from randomisation to any of: progression of disease prior to surgery, progression or recurrence of disease (as per BICR using Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1) after surgery, or death due to any cause. Patients who did not undergo surgery for reasons other than progression were considered to have an event according at RECIST version 1.1 progression or death.

Figure 1: Event-free survival (EFS) Kaplan-Meier curves - CM816

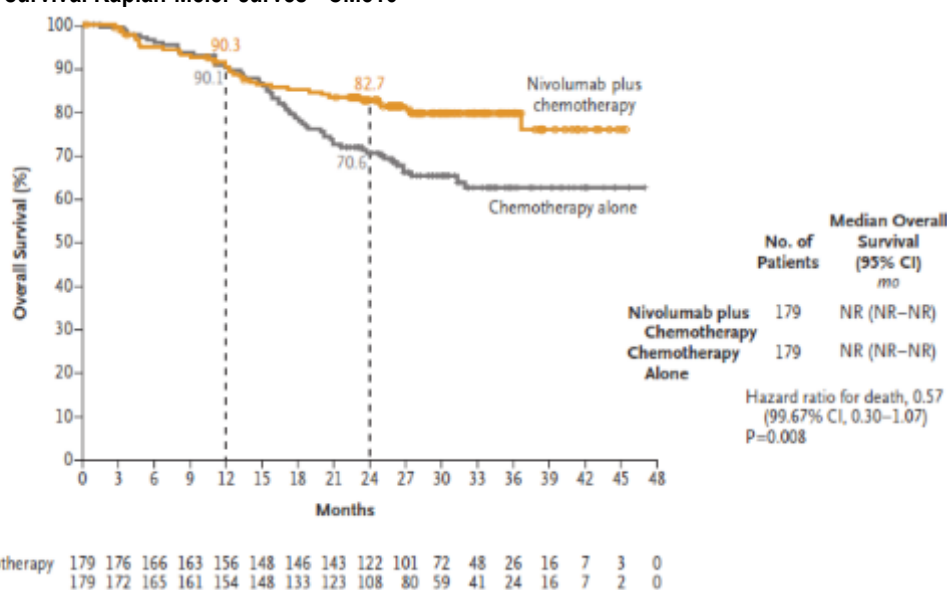


Source: Figure 13, p81 of the submission.

CI=confidence interval; EFS=event free survival; NR=not reached

- 6.13 Based on the pre-specified Interim analysis 1 of EFS (data cutoff 20 October 2021, median follow-up 29.5 months), neoNIVO+neoChemo was associated with a statistically significant improvement in EFS compared with neoChemo (median EFS 31.6 vs 20.8 months; HR = 0.63 (97.38% confidence interval [CI]: 0.43, 0.91); p-value = 0.0052). EFS rates (percentage of patients surviving without disease progression or disease recurrence) were higher in the neoNIVO+neoChemo arm than in the neoChemo arm at 12 months (76.1% versus 63.4%), and at 24 months (63.8% versus 45.3%).
- 6.14 There were 64/179 (35.8%) EFS events in the neoNIVO+neoChemo arm and 87/179 (48.6%) events in the neoChemo arm. The most common type of event in the neoNIVO+neoChemo and neoChemo arms was locoregional progression/recurrence after surgery: locoregional recurrences occurred in 13.4% and 15.6% of patients, respectively, and distant recurrences occurred in 7.8% and 14.0% of patients, respectively. Subgroup analyses of EFS are presented further below.
- 6.15 The OS results and corresponding KM curves are summarised in Figure 2.

Figure 2: Overall survival Kaplan-Meier curves - CM816



Source: Figure 14, p82 of the submission.

CI=confidence interval; NR=not reached

The p-value for overall survival did not cross the boundary for statistical significance (0.0033)

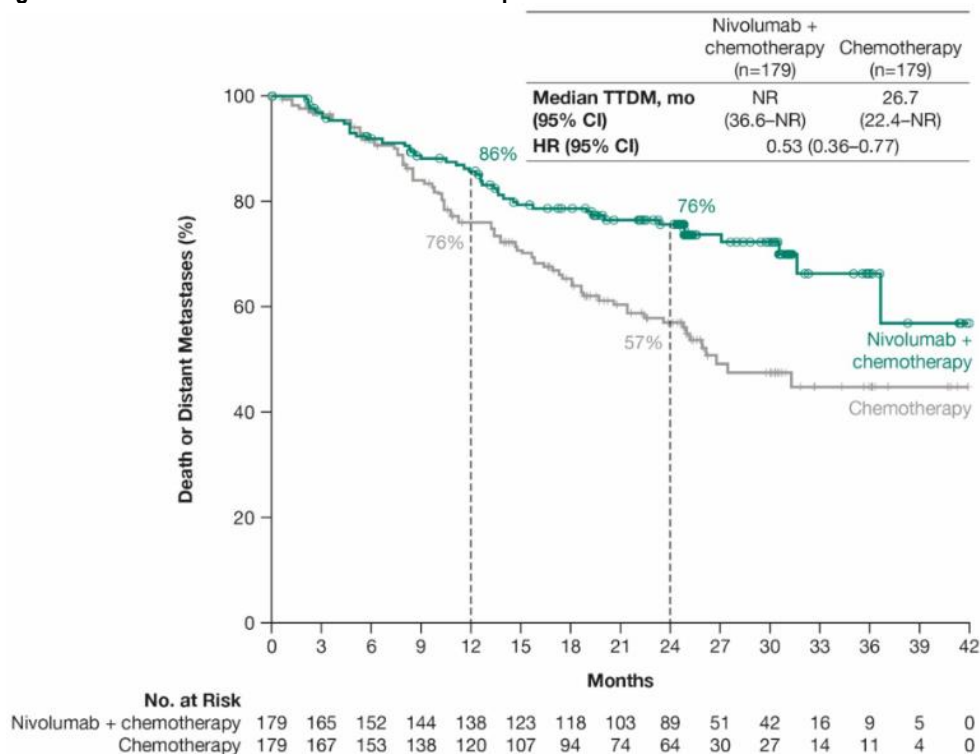
Number of events were not reported in the submission or in the CM816 clinical study report.

6.16 Based on the pre-specified Interim analysis 1, the OS data were immature at the October 2021 data cutoff. The number of events were not provided in the submission although median OS was not reached in either treatment arm. The KM curves were separated for the duration of follow-up favouring the neoNIVO+neoChemo arm. The point estimate of the reduction in hazard of death associated with neoNIVO+neoChemo, compared with neoChemo, was 43% which was not statistically significant¹⁵ (HR for death=0.57; [99.67% CI: 0.30, 1.07; p=0.008]). The PSCR provided the number of patients who died in CM816 (19.9% (35/176) in the neoNIVO+neoChemo arm and 33.5% (59/176) in the neoChemo arm).

6.17 Results for time to death or distant metastases (TTDM) are presented in Figure 3.

¹⁵ The adjusted (per Lan-DeMets alpha spending function) significance boundary for OS at interim analysis was 0.0033.

Figure 3: Time to death or distant metastases Kaplan-Meier curves - CM816



Source: Figure 15, p84 of the submission.

CI=confidence interval; mo=months; NR=not reached; TTD=Time to death or distant metastases

- 6.18 The neoNIVO+neoChemo arm was associated with a 47% reduction in the hazard of distant metastases or death compared to the neoChemo arm (HR=0.53; 95% CI: 0.36, 0.77). The submission noted that the benefit of neoNIVO+neoChemo in delaying distant metastases is likely contributing to the improvement in OS reported in the neoNIVO+neoChemo arm of CM816. The ESC considered that the composite endpoint of distant metastases or death was clinically meaningful for this patient group.
- 6.19 The percentage of patients with a pCR was 24.0% in the neoNIVO+neoChemo arm and 2.2% in the neoChemo arm (odds ratio [OR] =13.9; 99% CI: 3.5, 55.8; p<0.001). The percentage of patients with a major pathological response (MPR)¹⁶ was 36.9% in the neoNIVO+neoChemo arm and 8.9% in the neoChemo arm (OR=5.7; 99% CI: 3.2, 10.3).
- 6.20 Surgical outcomes in CM816 are summarised in Table 7.

¹⁶ Defined as the number of randomised patients with > 10% residual tumour in lung and lymph nodes as evaluated by BIPR, divided by the number of randomised patients for each treatment group.

Table 7: Summary of surgical outcomes - CM816

	neoNIVO+neoChemo (N=179)	neoChemo (N=179)
Patients with definitive surgery, n (%)	149 (83%)	135 (75%)
Time from last neoadjuvant dose to definitive surgery, weeks: Median (interquartile range: IQR)	5.3 (4.6–6.0)	5.0 (4.6–5.9)
Patients with cancelled definitive surgery, n (%), due to	28 (16%)	37 (21%)
Disease progression	12 (7%)	17 (10%)
Adverse event	2 (1%)	1 (0.6%)
Other	14 (8%)	19 (11%)
Patients with delayed surgery, n (%), due to	31 (21%)	24 (18%)
Administrative reason	17 (11%)	8 (6%)
Adverse event	6 (4%)	9 (7%)
Other	8 (5%)	7 (5%)
Length of delay in surgery, weeks: Median (IQR)	2.0 (0.6–3.0)	2.4 (1.0–3.7)
Of patients with delayed surgery, proportion with delay of, n (%)		
≤2 weeks	17 (55%)	11 (46%)
>2 and ≤4 weeks	8 (26%)	8 (33%)
>4 and ≤6 weeks	3 (10%)	2 (8%)
>6 weeks	3 (10%)	3 (13%)
Duration of surgery, minutes: Median (IQR)	185.0 (133.0–260.0)	213.5 (150.0–283.0)
Surgical approach, no (%)		
Thoracotomy	88 (59%)	85 (63%)
Minimally invasive ^a	44 (30%)	29 (22%)
Minimally invasive to thoracotomy	17 (11%)	21 (16%)
Type of surgery ^b , n (%)		
Lobectomy	115 (77%)	82 (61%)
Sleeve lobectomy	2 (1%)	10 (7%)
Bilobectomy	3 (2%)	4 (3%)
Pneumonectomy	25 (17%)	34 (25%)
Other	24 (16%)	21 (16%)
Completeness of resection ^c , n (%)		
R0 (no residual tumour)	124 (83%)	105 (78%)
R1 (microscopic residual tumour)	16 (11%)	21 (16%)
R2 (macroscopic residual tumour)	5 (3%)	4 (3%)
Rx (unknown)	4 (3%)	5 (4%)
Sampled lymph nodes — median (IQR)	19 (12–25)	18.5 (10–26)
Median length of hospital stay — days (IQR)	10.0 (7.0–14.0)	10.0 (7.0–15.0)

Source: Table 67, p103 of the submission and pp36-37 of Supplement to Forde et al., 2022.

IQR, interquartile range

^aThoracoscopic/robotic.

^bPatients may have had more than one surgery type

^cDenominator based on patients with definitive surgery (N=149 in the nivolumab plus chemotherapy group, N=135 in the chemotherapy group)

6.21 In the ITT population, 83.2% in the neoNIVO+neoChemo arm and 75.4% in the neoChemo arm underwent definitive surgery. Surgery was cancelled for 15.6% and 20.7% of patients in the neoNIVO+neoChemo and neoChemo arms, respectively. Reasons for cancellation included disease progression (6.7% and 9.5%, respectively), adverse events (AEs) (1.1% and 0.6%, respectively), and other reasons such as patient refusal and poor lung function (7.8% and 10.6%, respectively). Delayed surgery due to administrative reasons was double the amount in the neoNIVO+neoChemo arm

(11.4%) compared to the neoChemo arm (5.9%). The reason for this difference was not discussed in the submission.

- 6.22 In the neoNIVO+neoChemo arm, the median duration of surgery was numerically shorter (185 minutes vs. 213.5 minutes), the use of minimally invasive approaches was more common (29.5% vs. 21.5%), and pneumonectomies were less common (16.8% vs. 25.2%) compared with the neoChemo arm. Forde et al (2022)¹⁷ noted that these differences were more pronounced in patients with stage IIIA disease although these data were not provided in the publication or clinical study report.
- 6.23 Health-related QoL was assessed using the 3-level version of the EuroQol 5 Dimension (EQ-5D-3L) questionnaire. Baseline scores were high and similar between the treatment arms (range: 0.8859 to 0.8919). HRQoL was maintained from baseline in both the neoNIVO+neoChemo and neoChemo arms during the neoadjuvant treatment period. The submission concluded that the addition of nivolumab to chemotherapy in neoadjuvant use did not impact patient QoL compared to the use of chemotherapy alone.
- 6.24 Results for exploratory subgroup analyses of EFS in CM816, by PD-L1 expression (stratification factor at randomisation) are provided below:
- PD-L1 < 1%: HR = 0.85 (95% CI: 0.54, 1.32);
 - PD-L1 ≥ 1%: HR = 0.41 (95% CI: 0.24, 0.70);
 - PD-L1 1-49%: HR = 0.58 (95% CI: 0.30, 1.12); and
 - PD-L1 ≥ 50%: HR = 0.24 (95% CI: 0.10, 0.61).

The magnitude of the comparative EFS benefit associated with neoNIVO+neoChemo over neoChemo appeared to increase with increasing levels of PD-L1 expression. The EFS benefit in the high PD-L1 ≥ 50% expression subgroup may have been an important driver of that observed in the broader PD-L1 ≥ 1% population or the ITT population (HR 0.63; 95% CI: 0.45, 0.87).

- 6.25 A test for treatment effect variation (EFS) using the approach by Altman (2003)¹⁸, between the PD-L1 ≥ 1% and PD-L1 < 1% subgroups, yielded a statistically significant result (ratio of hazard ratios 0.48, 95% CI: 0.24, 0.96, p=0.04). A test for treatment effect variation (EFS) between the PD-L1 ≥ 50% and PD-L1 1-49% subgroups was not statistically significant, noting that this analysis lacked statistical power (ratio of hazard ratios 0.41, 95% CI: 0.14, 1.27, p=0.12).
- 6.26 Recognising the inherent caveats associated with subgroup analyses, the results suggest that the relative reduction in hazard of an EFS event, associated with

¹⁷ Forde PM, Spicer J, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *New England Journal of Medicine*. 2022;386(21):1973-85

¹⁸ Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*, 2003;326(7382):219.

neoNIVO+neoChemo over neoChemo, was larger for tumours that express PD-L1, especially those with high levels of PD-L1 expression ($\geq 50\%$).

- 6.27 The PSCR argued that the PD-L1 subgroup analyses support a conclusion of therapeutic benefit for neoNIVO+neoChemo versus neoChemo regardless of PD-L1 expression status on the basis that the point estimate of the EFS HR is less than 1.0 across all tested subgroups. The PSCR acknowledged that the upper bound of the 95% CI for some subgroups crosses 1.0 (PD-L1 < 1% and PD-L1 1-49%). However, the PSCR argued this did not support a conclusion of a lack of therapeutic benefit as the point estimate for EFS is in favour of neoNIVO+neoChemo and the CheckMate 816 trial was not designed or powered to detect a significant difference in EFS in these subgroups. The ESC agreed with the evaluation that the relative reduction in hazard of an EFS event for neoNIVO+neoChemo appeared larger for tumours that express PD-L1. The ESC also noted that PD-L1 expression was a stratification factor at randomisation and considered that the treatment arms were evenly matched for PD-L1 expression which likely reduced the potential for PD-L1 driven bias. However, the ESC considered that restricting access based on PD-L1 status may not be appropriate (see paragraph 3.8).
- 6.28 For the subgroup analysis of EFS by disease stage, the magnitude of relative EFS benefit associated with neoNIVO+neoChemo over neoChemo appeared more pronounced in patients with Stage IIIA disease (N=228, HR 0.54; 95% CI: 0.37, 0.80), compared to those with earlier Stage IB/II disease (N=127, HR 0.87; 95% CI: 0.48, 1.56). A test for treatment effect variation between the Stage IIIA versus Stage IB/II disease subgroups numerically favoured patients with Stage IIIA disease but was not statistically significant (ratio of hazard ratios 0.62, 95% CI: 0.31, 1.25). Interpretation of these results requires caution given the small sample size of the Stage IB/II disease subgroup. The PSCR stated the CheckMate 816 trial was not designed or powered to detect a significant difference in this subgroup. The ESC considered that whether neoadjuvant treatment with nivolumab is more effective in Stage IIIA disease, or whether earlier stage patients had insufficient time in the trial in which to recur, remains unclear.

Indirect treatment comparisons

- 6.29 The indirect comparisons between the CM816, NATCH, and IMpower010 trials were associated with a high risk of bias due to several differences across the trials in terms of patient, disease and study characteristics:
- The proportion of Asian patients differed substantially between the CM816 (52%) and IMpower010 (23%-26%) trials. The proportion of males differed across the CM816 (86%-88%), NATCH (approximately 71%), and IMpower010 (66%-67%) trials. The IMpower010 trial enrolled a higher proportion of never-smokers (23%) compared to the CM816 (11%) trial.
 - The proportion of patients with an ECOG PS of 0 was much higher for CM816 (approximately 70%) compared to NATCH (45%) and IMpower010 (54%-57%). On the other hand, the IMpower010 trial enrolled a relatively lower proportion of

patients with squamous histology (35%) compared to the NATCH and CM816 (49%-54%) trials.

- Recognising the different AJCC staging criteria (6th Edition NATCH versus 7th Edition for CM816 and IMpower010), important differences across the trials were noted in terms of the distribution of disease stage. CM816 enrolled the highest proportion of patients with Stage IIIA disease (64%) compared with NATCH ($\leq 2\%$) and IMpower010 (approximately 40%). As per protocol, the NATCH trial excluded patients with Stage IIIA N2 disease (AJCC 6th Edition). Notably, IMpower010 was based on pathological staging (post-surgery) while CM816 was based on clinical staging (pre-surgery).
 - Approximately 10% and 4% of patients enrolled in the IMpower010 trial had EGFR mutations and ALK alterations, respectively. There was limited information on EGFR/ALK status, gender, race, and smoking status in the NATCH trial. This is expected as the study was conducted in the early-to-mid 2000s. The applicability of the NATCH trial to current clinical practice, in terms of patient baseline risk, is also questionable.
- 6.30 Notably, whilst the proportion of patients who did not receive protocol-based treatments in CM816 and IMpower010 was small (approximately 2%), in NATCH, 34%, 6%, and 4% of patients randomised to the surgery+adjChemo, surgery alone, and neoChemo+surgery arms, respectively, did not receive the allocated treatment. Thus, the effectiveness of the adjChemo arm in NATCH was likely underestimated. These differences indicate there is important heterogeneity in treatment exposure and possibly treatment effects across the studies used for the ITCs.
- 6.31 The proportion of patients undergoing surgical resection was smaller in CM816 (75%-83%) than in NATCH (91%-96%). The clinical intent of surgical removal of tumour tissue is to prevent or delay disease recurrence or progression. The extent of impact of these differences on the comparative disease free survival (DFS) benefit is unclear.
- 6.32 The median duration of follow-up for the endpoint of DFS (NATCH, IMpower010) and EFS (CM816) varied across the included studies which ranged from 29.5 months in CM816 to 51 months in NATCH.
- 6.33 The indirect comparison between neoNIVO+neoChemo and adjChemo+adjATEZO involved substantial transformation or modelling of the observed data with several challenging underlying assumptions. The indirect comparison was also based on subgroups of patients from the CM816 and IMpower010 trials, that is, those with high-PD-L1 expressing NSCLC tumours ($\geq 50\%$). Importantly, NATCH, which linked the indirect comparison between CM816 and IMpower010, was conducted more than 20 years ago and did not assess PD-L1 status as there was no established evidence on this biomarker. NATCH was initiated in September 1999 compared to CM816 which was initiated in March 2017, and IMpower010 which was initiated in October 2015. The ITC between neoNIVO+neoChemo and adjChemo+adjATEZO was multistep based

on modelled data and several challenging assumptions which engender a high level of uncertainty associated with the indirect estimates of comparative benefit.

- 6.34 For the secondary comparator, adjChemo, the evidence was based on an anchored indirect comparison between the CM816 and NATCH trials (Bucher approach). The results are summarised in Table 8.

Table 8: Summary of results for neoadjuvant nivolumab plus chemotherapy versus adjuvant chemotherapy

Study drug	Trial ID	n/N with event (%)	Median time-to-event (95% CI)	Common reference n/N with event	Median time-to-event, months, (95% CI)	Hazard ratio (95% CI)
EFS from CM816 and DFS from NATCH						
neoNIVO+neoChemo vs neoChemo	CM816	<u>neoNIVO+neoChemo</u> 64/179 (36%)	31.6 (30.2, NA)	<u>neoChemo</u> 87/179 (49%)	20.8 (14.0, 26.7)	0.63 (0.45, 0.87)
neoChemo vs Surgery	NATCH	<u>neoChemo</u> 117/199 (58.8%)	NR	<u>Surgery</u> 132/210 (62.9%)	NR	0.92 (0.81, 1.04)
adjChemo vs Surgery	NATCH	<u>adjChemo</u> 125/210 (59.5%)	NR		NR	0.96 (0.75, 1.22)
adjChemo vs. neoChemo using surgery as common reference ^a	NATCH					1.04 (0.79, 1.37)
Indirect estimate of effect neoNIVO+neoChemo versus adjChemo using neoChemo as the common reference						0.60 (0.39, 0.93)
OS from CM816 and NATCH						
neoNIVO+neoChemo vs neoChemo	CM816	<u>neoNIVO+neoChemo</u> NR	NA	<u>neoChemo</u> NR	NR	0.57 (0.38, 0.87)
neoChemo vs Surgery	NATCH	<u>neoChemo</u> 99/199 (50%)	NR	<u>Surgery</u> 109/210 (52%)	NR	0.96 (0.84, 1.1)
adjChemo vs Surgery	NATCH	<u>adjChemo</u> 102/210 (49%)	NR		NR	0.99 (0.75, 1.3)
adjChemo vs. neoChemo using surgery as common reference ^a	NATCH					1.03 (0.76, 1.40)
Indirect estimate of effect neoNIVO+neoChemo versus adjChemo using neoChemo as the common reference						0.55 (0.33, 0.92)

Source: Table 59, p92 of the submission.

Adj=adjuvant; Chemo=chemotherapy; DFS=disease free survival; EFS=event free survival; NA=not available/not reached; neo=neoadjuvant; NIVO=nivolumab; NR=not reported; OS=overall survival.

^aNot provided in the submission but was derived during the evaluation to verify the final indirect estimates of treatment effect presented in the submission.

- 6.35 The indirect DFS hazard ratio indicated that neoNIVO+neoChemo was associated with a 40% reduction in the risk of recurrence or death compared to adjChemo (HR 0.60 [95% CI: 0.39, 0.93]).

- 6.36 Similarly, the indirect OS HR indicated that neoNIVO+neoChemo was associated with a 45% reduction in the risk of death compared to adjChemo (HR 0.55 [95% CI: 0.33, 0.92]).
- 6.37 No control for confounding through matching appears to have been conducted, despite differences in patient and disease characteristics between the trials as discussed previously. Recognising these limitations associated with cross-trial comparisons, however, the totality of the evidence indicated that neoNIVO+neoChemo may be superior to adjChemo in different treatment lines. The evidence however remains inadequate to enable a robust quantification of the magnitude of comparative benefit.
- 6.38 For the supplementary comparator adjChemo+adjATEZO, the submission noted that there were several important differences between the CM816 and IMpower010 trials which limited the applicability of the Bucher or other standard ITC methodologies:
- Lack of “interchangeability” between the treatment settings and measurement of EFS/DFS across the trials due to differences in when patients were randomised to treatment, relative to diagnosis, and initiation of anti-cancer treatment.
 - Patients in CM816 were randomised before neoadjuvant treatment and therefore before surgery. In IMpower010, patients who had a complete resection and received 1 to 4 cycles of adjuvant chemotherapy were randomised to receive atezolizumab or best supportive care (BSC).
- 6.39 A “Time-to-event” and “Mixture model” framework was used to conduct the ITC. The time-to-event framework is summarised in Table 9. EFS/DFS hazards associated with neoNIVO+neoChemo and adjChemo+adjATEZO were subsequently derived which varied over time due to:
- Time-varying HR inputs for neoChemo versus adjChemo from NATCH (Step 3 of time-to-event framework);
 - The 7-month ‘offset’ before applying the benefit from receiving atezolizumab (Step 4 of time-to-event framework); and
 - The use of a mixture model after 7 months was used to adjust for a proportion of patients (assumed in the submission to be 20%) who would be considered eligible to enrol in CM816, and who would be alive and event-free in the adjuvant setting, but yet ineligible to receive adjuvant atezolizumab in the IMpower010 trial (such as patients with incomplete resection, incomplete adjuvant chemotherapy, and contraindications or refusal).

Table 9: Time-to-event framework applied in the indirect treatment comparison: CM816 and IMpower010

Step	Methods
1	Kaplan-Meier EFS curves from PD-L1 subgroups from CM816 were generated. Proportional hazards assumption was tested using visual inspection of Kaplan-Meier curves, log cumulative hazard plots, Schoenfeld residuals, and the Grambsch-Therneau test. The assumption of proportional hazards was not rejected.
2	Parametric survival models were fit to the neoadjuvant chemotherapy arm. The best fitting model per Akaike Information Criteria, Bayesian information criteria and clinical plausibility of fit was deemed to be Log-normal. The EFS curve for nivolumab plus chemotherapy was applied using the EFS HR reported in CM816 to the Log-normal model of neoadjuvant chemotherapy.
3	Kaplan-Meier curves from the neoadjuvant chemotherapy and adjuvant chemotherapy arms of the NATCH trial were digitised. The p-value of the Grambsch-Therneau test was 0.02, indicating that the null hypothesis of proportional hazards was rejected, statistically. Visual inspection suggested a stronger initial treatment effect favouring neoadjuvant chemotherapy that waned over time. To address this issue, a piecewise constant hazard ratio approach was used, with HRs estimated separately for: 0 to 7 months and 7 months to end of follow-up. These piecewise constant HRs were applied to the neoadjuvant chemotherapy arm (separately, for < 7 months, and ≥ 7 months) to generate a DFS curve for adjuvant chemotherapy.
4	The DFS HR for atezolizumab versus BSC from IMpower010 was applied to the adjuvant chemotherapy DFS curve derived above starting at 7 months. The initial 7-month period was estimated as the time between randomisation in CM816 and IMpower010. In this 7-month period patients would undergo surgery and receive 4 doses of adjuvant chemotherapy prior to be eligible to be randomised to receive atezolizumab in IMpower010.
5	In the time-to-event framework the atezolizumab DFS curve followed the adjuvant chemotherapy curve for the first 7 months, and thereafter the DFS HR for atezolizumab versus BSC was applied.

Source: Table 64, pp99-100 of the submission.

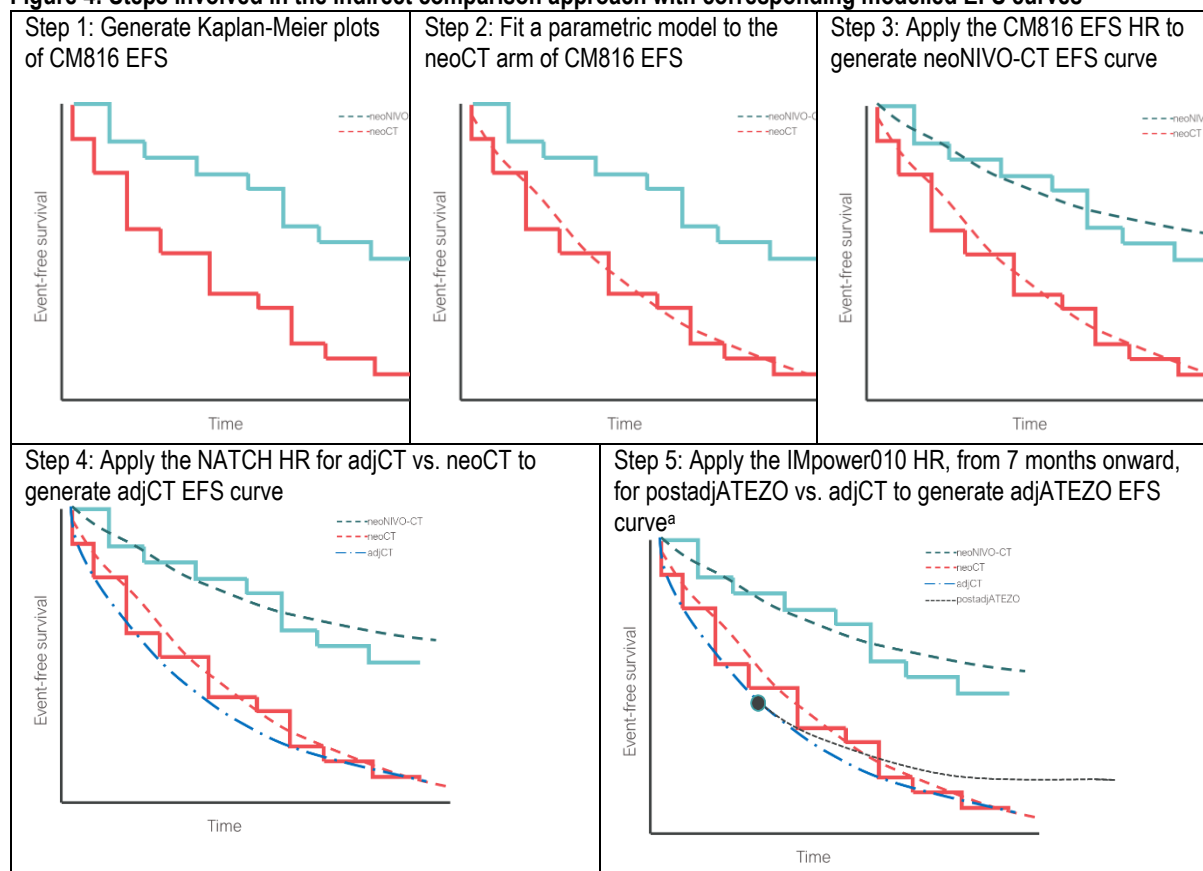
BSC=best supportive care; DFS=disease free survival; EFS=event free survival; HR=hazard ratio; PD-L1=programmed cell death Ligand-1

6.40 The 7-month duration (30 weeks) was based on historical studies, clinical expert advice from the sponsor’s advisory board, and several assumptions that were difficult to verify, but was derived as follows:

- Time from diagnosis/trial enrolment to surgery: 4 weeks;
- Time from surgery to adjChemo initiation: 9 weeks;
- Duration of adjChemo (time to the last dose): 14 weeks; and
- Completion of adjChemo to initiation of atezolizumab: 3 weeks.
- Total 30 weeks.

6.41 The steps involved in the indirect comparison approach with corresponding modelled EFS curves are illustrated in Figure 4. Essentially, this modelled approach ignores the major transitivity issues across the trials and the contribution of the observed data in the ITC appears minimal.

Figure 4: Steps involved in the indirect comparison approach with corresponding modelled EFS curves



Source: Figure 5, p23 of the indirect comparison technical report, Attachment 5 accompanying the submission.

adjCT=adjuvant chemotherapy; EFS=event-free survival; HR=hazard ratio; neoCT=neoadjuvant chemotherapy; neoNIVO-CT=neoadjuvant nivolumab plus chemotherapy; postadjATEZO=adjuvant atezolizumab following adjuvant CT.

^a Prior to 7 months, the adjATEZO curve follows the adjCT curve

6.42 Results of the indirect comparisons are summarised in Table 10.

Table 10: Modelled indirect comparison of EFS/DFS between neoNIVO+neoChemo versus adjChemo+adjATEZO – patients with Stage II-IIIa, PD-L1 ≥ 50%

Time period ^a	Description	neoNIVO+neoChemo vs. adjChemo+adjATEZO, HR (95% CI)
0-36 months	Full time horizon	0.29 (0.11, 0.75)
0-7 months	Period before to ATEZO initiation	0.16 (0.05, 0.46)
7-36 months	Period after ATEZO initiation	0.44 (0.15, 1.24)

Source: Table 66, p102 of the submission

adjChemo=adjuvant chemotherapy; adjATEZO=adjuvant atezolizumab; CI=confidence intervals; DFS=disease free survival; EFS=event free survival; HR=hazard ratio; neoNIVO+neoChemo=neoadjuvant nivolumab plus chemotherapy; PD-L1= programmed cell death ligand 1.

^aThe 36-month period was sub-divided into the period pre-atezolizumab initiation (0 to < 7 months) and post-atezolizumab initiation (7 to 36 months).

6.43 The ITC was complex, with substantial modelling or adjustment of the observed data, and was based on several untested assumptions. The modelled ITC approach essentially ignored the several differences in study design, patient, and disease characteristics across the CM816, NATCH, and IMpower010 trials. Therefore, the evaluation concluded that no firm conclusions could be made on the direction and magnitude of comparative effectiveness between the neoadjuvant use of nivolumab

and adjuvant use of atezolizumab in NSCLC. The pre-PBAC response argued that the ITC made use of the best available evidence and acknowledged the limitations compared to a traditional Butcher ITC.

Comparative harms

6.44 A summary of overall adverse events (AEs) in CM816 is presented in Table 11. Frequently reported treatment-related AEs ($\geq 15\%$ of patients in any treatment arm) in CM816 are summarised in Table 12.

Table 11: Summary of adverse events reported in CM816

	neoNIVO+neoChemo (N=176)	neoChemo (N=176)	RR (95% CI), p-value
Any adverse event (all-cause)	163 (93%)	171 (97%)	0.95 (0.90, 1.0), p=0.05
Any adverse event \geq Grade 3 (all-cause)	72 (41%)	77 (44%)	0.93 (0.73, 1.2), p=0.58
Adverse events resulting in treatment discontinuation (all-cause)	18 (10%)	20 (11%)	0.90 (0.49, 1.6), p=0.73
Adverse events resulting in treatment discontinuation (treatment-related)	18 (10%)	17 (10%)	1.06 (0.56, 2.0), p=0.85
Deaths due to treatment-related toxicity ^a	0	3 (2%)	0.14 (0.001, 2.7), p=0.20
Surgery related adverse events ^b	62/149 (42%)	63/135 (47%)	0.89 (0.69, 1.16), p=0.39

Source: Table 68, pp104-105 of the submission.

Chemo=chemotherapy; neo=neoadjuvant; NIVO=nivolumab; RR=relative risk.

Adverse events were coded using the worst grade per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 criteria by system organ class and preferred term based on Medical Dictionary for Regulatory Activities (MedDRA) terminology v 24.0.

^aTreatment-related deaths in the chemotherapy-alone group were due to pancytopenia, diarrhoea, acute kidney injury (all in one patient), enterocolitis, and pneumonia.

^bThe denominators are based on patients who underwent definitive surgery. Included are events reported up to 90 days after definitive surgery.

Table 12: Frequently reported treatment-related adverse events ($\geq 15\%$ of patients in any treatment arm) - CM816

	neoNIVO+neoChemo (N=176)		neoChemo (N=176)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse events	145 (82%)	59 (34%)	156 (89%)	65 (37%)
Nausea	58 (33%)	1 (1%)	73 (42%)	1 (1%)
Anaemia	42 (24%)	5 (3%)	40 (23%)	6 (3%)
Constipation	37 (21%)	0	36 (21%)	2 (1%)
Decreased appetite	29 (17%)	2 (1%)	38 (22%)	4 (2%)
Neutropenia	28 (16%)	15 (9%)	29 (17%)	21 (12%)
Decreased neutrophil count	26 (15%)	13 (7%)	37 (21%)	19 (11%)

Source: Table 69, p105 of the submission.

Chemo=chemotherapy; neo=neoadjuvant; NIVO=nivolumab

6.45 The rates of any AE (all cause), AE of Grade ≥ 3 , and AEs resulting in treatment discontinuation (all-cause or treatment-related), were similar between the treatment arms. AEs of any grade that were identified as surgical complications occurred in 42% of patients in the neoNIVO+neoChemo arm and in 47% of patients in the neoChemo arm. There were no deaths due to drug-related toxicity in the neoNIVO+neoChemo arm and 3 deaths (2%) in the neoChemo arm.

6.46 For the neoNIVO+neoChemo versus the neoChemo arms, the most common Grade 3-4 treatment-related AEs were neutropenia (9% versus 12%).

- 6.47 The most frequently reported immune-mediated AEs (IMAEs) reported for patients treated with neoNIVO+neoChemo were: rash (9%); hyperthyroidism (4%); and hypothyroidism/thyroiditis (2%). The nature of these IMAEs is consistent with the established IMAE profile of nivolumab. See Table 15 for details.
- 6.48 Overall, in the CM816 trial, the addition of nivolumab to chemotherapy is expected to result in an increased risk of immune checkpoint-related AEs. The safety data were consistent with the established safety profiles of these agents. The risk of IMAEs in the real world is expected to be higher than that in the experimental setting.
- 6.49 The indirect comparisons of safety were descriptive and inadequate to support any conclusive claim on comparative safety. The indirect comparison of safety between neoNIVO+neoChemo versus adjChemo is presented in Table 13.

Table 13: Frequently reported adverse events (≥ 15% in either treatment arm) – CM816 and NATCH

	CM816				NATCH			
	neoNIVO+neoChemo (N=176)		neoChemo (N=176)		neoChemo (N=193)		adjChemo (N=139)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Nausea	58 (33%)	1 (0.6%)	73 (42%)	1 (0.6%)	38 (20%)	3 (2%)	44 (32%)	4 (3%)
Anaemia	42 (24%)	5 (3%)	40 (23%)	6 (3%)	76 (39%)	1 (0.5%)	59 (42%)	2 (1%)
Constipation	37 (21%)	0	36 (21%)	2 (1%)	NR	NR	NR	NR
Decreased appetite	29 (17%)	2 (1%)	38 (22%)	4 (2%)	NR	NR	NR	NR
Neutropenia	28 (16%)	15 (9%)	29 (17%)	21 (12%)	62 (32%)	24 (12%)	38 (27%)	10 (7%)

Source: Table 72, p108 of the submission.

Adj=adjuvant; Chemo=chemotherapy; neo=neoadjuvant; NIVO=nivolumab

- 6.50 AE rates varied substantially between the neoChemo common reference arms of the CM816 and NATCH trials reflecting the different patient populations and treatment exposure. Higher rates of nausea were reported in CM816, while higher rates of anaemia and neutropenia were reported in NATCH. Nausea, anaemia and neutropenia are well established side effects associated with the use of the chemotherapy agents which were administered in both trials. The indirect comparison of safety between the CM816 and NATCH trials ignores the additional incidence of IMAEs associated with neoadjuvant immunotherapy with nivolumab.
- 6.51 The comparison of safety between neoNIVO+neoChemo and adjChemo+adjATEZO are presented in Table 14 and Table 15.

Table 14: Comparison of overall adverse events reported in CM816 and IMpower010

	CM816	IMpower010
	neoNIVO+neoChemo (N=176)	adjChemo+adjATEZO (N=495)
Any adverse event (all-causality)	163 (93%)	459 (93%)
Any adverse event ≥ Grade 3 (all-causality)	72 (41%)	116 (25%)
Adverse events resulting in treatment discontinuation (all-causality)	18 (10%)	90 (18%)
Adverse events resulting in treatment discontinuation (study drug-related)	18 (10%)	NR
Deaths due to study drug toxicity	0	8 (2%)

Source: Table 74, p109 of the submission.

Adj=adjuvant; ATEZO=atezolizumab; Chemo=chemotherapy; neo=neoadjuvant; NIVO=nivolumab

Table 15: Comparison of immune mediated adverse events: CM816 and IMpower010

Immune mediated adverse event	CM816	IMpower010
	neoNIVO+neoChemo (N=176)	adjChemo+adjATEZO (N=495)
Adrenal insufficiency	1%	1%
Rash	9%	18%
Hyperthyroidism	4%	7%
Hypothyroidism/thyroiditis	2%	17%
Pneumonitis	1%	4%

Source: Tables 76-77, pp110-111 of the submission.

Adj=adjuvant; ATEZO=atezolizumab; Chemo=chemotherapy; neo=neoadjuvant; NIVO=nivolumab

6.52 Overall AEs and IMAEs were generally more frequent in the adjChemo+adjATEZO arm compared with neoNIVO+neoChemo. Interpretation of the safety data should consider 1) the longer exposure to adjuvant atezolizumab (median 16 cycles or one year) compared to that of neoadjuvant nivolumab (maximum of three cycles), and ii) the different eligible trial populations across neoadjuvant use and adjuvant use.

Benefits/harms

6.53 A summary of the comparative benefits and harms for neoNIVO+neoChemo compared with neoChemo is presented in Table 16.

Table 16: Summary of comparative benefits and harms – CM816

	Nivolumab, 360 mg Q3W plus chemotherapy Q3W Maximum 3 cycles	Chemotherapy Q3W Maximum 3 cycles
Interim analysis 1; Data cutoff October 2021; Median duration of follow up 29.5 months.		
Benefits^a: EFS		
Intention to treat Stage IB-IIIa NSCLC (American Joint Committee on Cancer 7th Edition)		
	N=179	N=179
Events ^a , n (event rate per 100 patients, %)	64 (35.8)	87 (48.6)
Median EFS duration, months (95% CI)	31.6 (30.2, NA)	20.8 (14.0, 26.7)
HR (95% CI); p-value	0.63 (0.45, 0.87); p-value=0.0052^b	
EFS rate at 24 months, %	63.8	45.3
Difference, %	18.5	
Subgroup stratification factor: Stage IIIa NSCLC^c		
	N=113	N=115
Events ^a , n (event rate per 100 patients, %)	43 (38.1)	62 (53.9)
Median EFS duration, months (95% CI)	31.6 (26.6, NA)	15.7 (10.8, 22.7)
HR (95% CI)	0.54 (0.37, 0.80)	
Subgroup stratification factor: PD-L1 ≥ 1%^d		
	N=89	N=89
Events ^a , n (event rate per 100 patients, %)	21 (23.6)	41 (46.1)
Median EFS duration, months (95% CI)	NA	21.1 (11.5, NA)
HR (95% CI)	0.41 (0.24, 0.70)	
Subgroup PD-L1 ≥ 50%		
	N=38	N=42
Events ^a , n (event rate per 100 patients, %)	6 (15.8)	20 (47.6)
Median EFS duration, months (95% CI)	NA	19.7 (8.2, NA)
HR (95% CI)	0.24 (0.10, 0.61)	
Harms^e: (event rate per 100 patients), Safety evaluable population		
Immune mediated adverse events, any grade	N=176	N=176
Rash, n (%)	15 (8.5)	1 (0.6)
Difference	7.9%	
Hyperthyroidism, n (%)	7 (4.0)	0 (0.0)
Difference	4.0%	

Source: Section 2.5 of the submission and Section 7.2 of the CM816 Clinical Study Report.

CI=confidence interval; chemo=chemotherapy; EFS=event free survival; HR=hazard ratio; NSCLC=non-small cell lung cancer; n=number of patients; NA=not reached/not available; NIVO=nivolumab; PD-L1 programmed cell death ligand 1.

^aOverall survival data remain immature at the data cutoff date October 2021. Events were also not provided. Thus only EFS is presented: EFS was defined as time from randomisation to progression of disease precluding surgery, progression or recurrence of disease after surgery, or death due to any cause.

^bStratified log-rank test p-value = 0.0052. The p-value threshold for statistical significance at interim analysis was 0.0262.

^cStage IIIa versus Stage 1B-II.

^dPD-L1 < 1% versus PD-L1 ≥ 1% or not evaluable.

^eThere were no important differences between treatment arms in terms of overall adverse events, frequently reported adverse events (≥ 15% of patients in any treatment arm), and ≥ 3 Grade immune-mediated adverse events. Thus, only immune-mediated adverse events of any grade have been presented.

Bolded results are statistically significant

6.54 On the basis of the CM816 trial, for every 100 patients with resectable NSCLC, treated with nivolumab 360 mg Q3W and chemotherapy (Q3W) for 3 cycles versus chemotherapy alone, over a median follow up of 19.5 months:

- In the overall Stage 1B-IIIa NSCLC population, 19 additional patients will remain event free (defined as ‘any progression of disease precluding surgery, progression

or recurrence of disease after surgery, progression of disease in the absence of surgery, or death from any cause') at 2 years. The reduction in hazard of an event occurring is 37%.

- Approximately 8 additional patients will experience any grade rash and 4 additional patients will experience any grade hyperthyroidism.

6.55 The results of the unadjusted ITCs were unreliable and associated with a high risk of bias, particularly the modelled ITC with adjChemo+adjATEZO. There were several important differences in patient, disease and other study characteristics that were not adjusted for. The impact of unknown confounders remains unclear. All these limitations lead to a high level of uncertainty regarding the magnitude of any incremental benefit associated with neoNIVO+neoChemo compared with either adjChemo or adjChemo+adjATEZO. Interpretation of the safety data was problematic given the descriptive nature of the comparisons. Furthermore, the ITCs have not been captured in the economic analysis and financial estimates. Accordingly, a benefits/harms quantification table for the ITCs has not been presented.

Clinical claim

6.56 The submission described neoNIVO+neoChemo as:

- Superior in terms of effectiveness (EFS) and non-inferior in terms of safety compared with neoChemo;
- Superior in terms of effectiveness (EFS) and non-inferior in terms of safety compared with adjChemo; and
- 'Likely superior and at least non-inferior' in terms of effectiveness (EFS) and 'different and non-inferior' in terms of safety compared with adjChemo+adjATEZO.

6.57 The evaluation considered the therapeutic conclusion regarding the direct comparison with neoChemo, in terms of EFS, was supported by the clinical evidence presented in the submission. Interim OS data from CM816 were immature at the October 2021 data cutoff although the results favoured neoNIVO+neoChemo over neoChemo (HR for death=0.57; 99.67% CI: 0.30, 1.07; p=0.008). The ESC considered that the claim of superior comparative effectiveness for neoNIVO+neoChemo versus neoChemo was supported by the data presented for EFS and also for the clinically meaningful composite endpoint of death or distant metastases.

6.58 The evaluation considered comparative safety was slightly worse with neoNIVO+neoChemo compared to neoChemo in terms of IMAEs but manageable. The ESC considered the claim of non-inferior safety was not supported by the clinical evidence provided in the submission.

6.59 Regarding the indirect comparison with adjChemo, transitivity was questionable given the differences in study, patient and disease characteristics across the CM816 and NATCH trials. The evidence remains inadequate to enable a robust quantification of

the magnitude of comparative benefit. Notwithstanding these limitations, and recognising the need for caution in cross-study comparisons, the evaluation considered the totality of the evidence indicated neoNIVO+neoChemo may be superior to adjChemo. The ESC considered the claim of superior effectiveness compared to adjChemo was uncertain due to the transitivity concerns identified for the indirect comparison. The ESC also considered the claim of non-inferior safety was uncertain.

- 6.60 The comparison between neoNIVO+neoChemo and adjChemo+adjATEZO involved different treatment settings with differences in the eligible patient populations (potentially resectable patients, as assessed prior to surgery, in neoadjuvant use versus patients with completely resected tumours following adjChemo in adjuvant use). The submission made a comprehensive effort to address some of these contextual differences. However, the ITC was particularly complex, with substantial modelling and adjustment of the observed trial data. The evaluation considered the therapeutic conclusion regarding the indirect comparison with adjChemo+adjATEZO was not adequately supported. No firm conclusions can be made on the modelled ITC results as much of the observed data were adjusted and several untested assumptions were made. Importantly, no measures to address the differences in patient and disease characteristics across the trials in the ITC were undertaken. The ESC considered that the ITC limitations outlined lead to a high level of uncertainty regarding the magnitude of any incremental benefit associated with neoNIVO+neoChemo compared with adjChemo+adjATEZO. The ESC also considered the claim of non-inferior safety with adjChemo+adjATEZO was uncertain.
- 6.61 The PBAC considered that the claim of superior comparative effectiveness compared to neoChemo was reasonable. The PBAC considered the claim of non-inferior comparative safety compared with neoChemo was not adequately supported by the data.
- 6.62 The PBAC considered the claim of superior comparative effectiveness and non-inferior safety compared to adjChemo was not adequately supported by the data.
- 6.63 The PBAC considered the claim of 'likely superior and at least non-inferior' effectiveness and 'different and non-inferior' safety compared with adjChemo+adjATEZO was not adequately supported by the data.

Economic analysis

- 6.64 The submission presented a stepped economic evaluation based on the direct randomised trial CM816. The economic evaluation compared neoNIVO+neoChemo versus neoChemo for the treatment of patients with resectable (tumours \geq 4 cm or node positive) NSCLC. The key components of the economic evaluation are summarised in Table 17.

Table 17: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	neoadjuvant nivolumab + chemotherapy versus neoadjuvant chemotherapy
Time horizon	25 years in the model base case versus median follow-up of 29.5 months in the key trial CM816
Outcomes	Life years (LYs) gained and quality-adjusted life years (QALYs) gained
Methods used to generate results	Semi-Markov cohort model
Health states	Four health states: event-free survival (EFS), locoregional recurrence (LR), distant metastasis (DM) and death
Cycle length	3 weeks
Transition probabilities	<p>Transition probabilities from EFS to other health states (LR, DM and death) and the transition probabilities from LR to death were estimated based on the Kaplan-Meier data on time to LR, time to any progression, mortality in event-free patients and post-LR survival from Trial CM816.</p> <p>The submission assumed a constant transition probability from LR to DM over the entire time horizon, based on clinician opinion.</p> <p>DM health state was modelled as an absorbing health state. One-off costs, LYs and QALYs were applied on transition.</p> <p>Health outcomes associated with various treatments for metastatic NSCLC were estimated 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.</p>
Extrapolation method	<p>Jointly fitted log-normal distributions were used to extrapolate time to LR and time to any progression from Month 25. Survival data in event-free patients were pooled for the two treatment arms and extrapolated using an exponential function from Month 25 (around 20%-30% patients remaining at risk). The spline model (DF = 3, hazard) was used to extrapolate post-LR survival data from Month 21 (around 20% patients remaining at risk).</p> <p>Adjustment for a cure assumption has been incorporated into the transitions from EFS to LR and to DM. It was assumed that, in both treatment arms, the proportion of patients in the EFS health state who were cured linearly increased from Year 5 to a maximum of 95% at Year 7.</p> <p>All extrapolations were adjusted for background mortality.</p>
Health related quality of life	<p>Health state utilities for EFS and LR were derived from CM816 and adjusted based on the utility in general Australian population reported in an external study (Clemens <i>et al</i> 2014). EFS =0.85; LR = 0.796</p> <p>Health state utility for DM was not estimated specifically. Instead, one-off QALYs (1.357 QALYs) were applied on transition and the estimates were sourced from previous PBAC submissions (see the "Transition probabilities" row above).</p>

Source: Table 85, p121 of the submission.

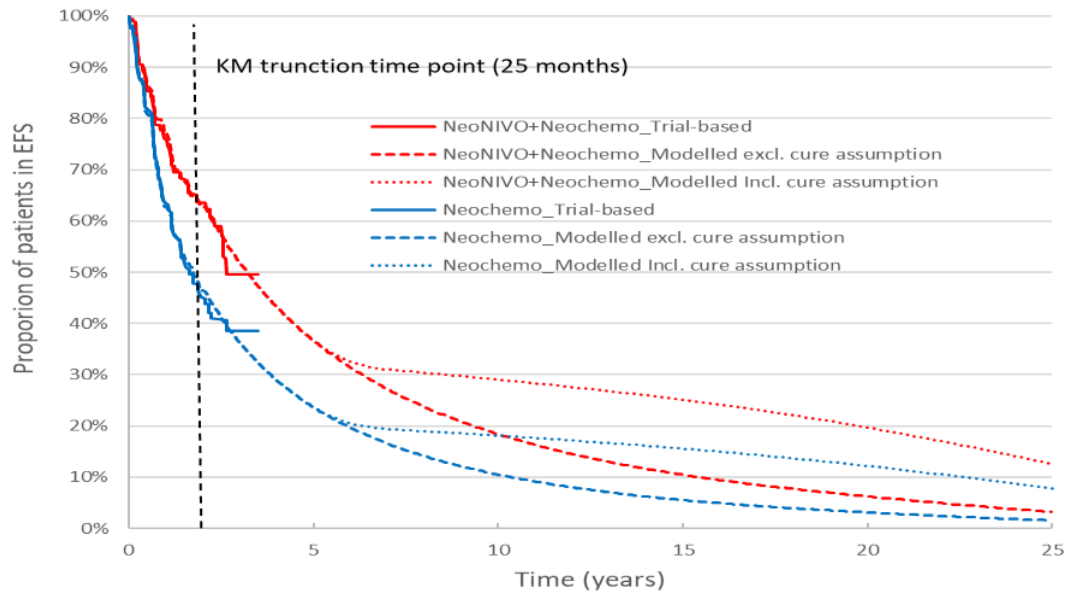
DF = degrees of freedom; DM = distant metastasis; EFS = event-free survival; LYs = life years; LR = locoregional recurrence; NSCLC = non-small cell lung cancer; PSD = Public Summary Document; QALYs = quality-adjusted life years

6.65 The economic model adopted a 25-year time horizon, compared with a median follow-up of 29.5 months in CM816. The same time horizon was used in the previous PBAC submission of atezolizumab as adjuvant treatment for patients with Stage II-IIIa, PD-L1 positive NSCLC following complete resection and platinum-based chemotherapy. In March 2022, the ESC considered that a better prognosis (in comparison with use in locally advanced unresectable NSCLC and metastatic disease) might justify a longer time horizon, however the trial data did not provide a reliable basis for a long-term

extrapolation. At that time the PBAC agreed with ESC that, based on the duration of follow-up in the clinical trial (median follow-up of 32.2 months in the key atezolizumab trial IMpower010) and the extent of extrapolation required, a 15-year time horizon was more reasonable in this population (Paragraphs 6.36, 6.37, and 7.7, atezolizumab Public Summary Document [PSD], March 2022 PBAC meeting). The PSCR acknowledged the potential uncertainty in the long-term extrapolation based on the median trial follow-up period of 29.5 months in the CM816 clinical trial but argued that using a shorter time horizon would fail to sufficiently capture the full cost and benefit associated with the treatment of patients with resectable NSCLC. The ESC considered that the logic applied to the economic evaluation of atezolizumab in March 2022 was relevant to the current submission and advised that a 15-year time horizon was likely appropriate. The pre-PBAC response noted that data from a patient-level meta-analysis, conducted by the sponsor, of patients with stage I to III NSCLC receiving neoadjuvant therapy suggested that 19% of the patients were still alive after 15 years and therefore argued that using a 15-year time horizon would fail to capture the full cost and benefits associated with patients entering the model.

- 6.66 The KM curves for EFS in the CM816 clinical trial were not used in the economic evaluation. Instead, trial-based time to locoregional recurrence (LR) was the basis to estimate the transition probabilities from EFS to LR following neoNIVO+neoChemo and following neoChemo. As data on time to distant metastasis (DM) from CM816 were immature with only 20 DM events occurring in the neoNIVO+neoChemo arm (11.2%), and 32 DM events in the neoChemo arm (17.9%), transitions from EFS to DM were calculated as the difference between the time to any progression and time to LR. The survival curves in event-free patients for both treatment groups were overlapping during the trial observation period. Therefore, data on death from the two treatment arms prior to recurrence were pooled to estimate the transition probabilities from EFS to death. A comparison of the trial KM data on EFS and the modelled proportion of patients remaining in the EFS health state over time is presented in Figure 5. The evaluation considered that the modelled EFS estimates provided a reasonable fit to the trial-based data, based on visual inspection.

Figure 5: Trial-based versus modelled EFS



Source: Figure constructed during the evaluation from the “Attachment 7 - Nivolumab neoadjuvant NSCLC Economic Evaluation” Excel workbook

EFS = event-free survival; KM = Kaplan-Meier; neoChemo = neoadjuvant chemotherapy; neoNIVO = neoadjuvant nivolumab

- 6.67 Trial data on time to LR, time to any disease progression, and time to death in event-free patients, were truncated at a time point when at least 20% of patients were at risk in either arm in the trial. The PBAC guidelines (version 5.0) recommend the use of observed time-to-event data in preference to modelled data up to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free. The method the submission used to determine the point at which KM data were truncated invoked a switch to extrapolated methods while there were still reasonable patient numbers in some arms. However, sensitivity analyses conducted during the evaluation showed that the results of the economic model were not sensitive to the use of alternative extrapolation time points.
- 6.68 Parametric model selection was based on an assessment of proportional hazards, goodness of fit statistics, visual inspection and assessment of clinical plausibility. The submission claimed that diagnostic plots, e.g. the log-log plot and the Schoenfeld residuals, suggest that the proportional hazard assumption holds between the two arms for both time to disease progression curves and time to any progression curves; therefore, a jointly fitted approach was adopted. The interpretation of the diagnostic plots is not as straightforward as suggested by the submission. The log-log survival curve after 10 months was not a continuation of the first 10 months, and the Schoenfeld residuals plot, while flattened for the first 10 months, showed a non-zero slope from 11 months and crossed 0 at around 27-28 months. This does not support use of jointly fitted models, which effectively assumed ongoing treatment effect (in terms of time to LR and time to any disease progression) throughout the entire 25-year time horizon following the short treatment duration of neoNIVO+neoChemo or neoChemo in neoadjuvant use (up to 3 treatment (3-weekly) cycles). The impacts of

using independent parametric functions, to extrapolate time to LR data and time to any progression data for neoNIVO+neoChemo and for neoChemo, on the incremental cost-effectiveness ratio (ICER) could not be estimated during the evaluation as the submission did not provide the scale and shape parameters for independent distributions.

- 6.69 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. A comparison of modelled EFS curves with and without incorporating a cure rate (Figure 5) indicates that this adjustment resulted in sustained EFS benefit to approximately 20 years, after which the EFS curves of the two treatments converged due to background mortality. The submission argued that the application of a cure assumption was supported by the long-term EFS data from external studies which show a plateau after approximately 5 years¹⁹. However, all the interventions in these external studies were neoChemo, and did not include the concomitant use of neoNIVO. The submission noted that a cure assumption was included in two National Institute for Health and Care Excellence (NICE) Technology Appraisals (TAs) on adjuvant treatments following complete resection of early stage NSCLC. In the osimertinib (TA761) model, it was assumed that 95% of patients who were recurrence-free at 5 years would be cured. Clinical expert advice to the NICE Evidence Review Group (ERG) was that, for the active monitoring arm of the model, a 5-year cure time point may be appropriate, however a potential cure time point for the intervention arm was considered uncertain. The ERG did an additional analysis applying a later time point for cure (8 years) in the adjuvant osimertinib group. The atezolizumab (TA823) model developed by the sponsor used a cure rate of 91.5% at Year 5. The NICE Appraisal Committee noted that there was uncertainty around both the cure time point and the proportion cured. The Committee considered that a cure time point of 6 years or 7 years for atezolizumab and a cure time point of 5 years for active

¹⁹ Pless M, Stupp R, *et al.* Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet*. 2015;386(9998):1049-56

Felip E, Rosell R, *et al.* Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *Journal of Clinical Oncology*. 2010;28(19):3138-45.

Scagliotti GV, Pastorino U, *et al.* Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. *Journal of Clinical Oncology*, 2012;30(2), 172–178.

Pisters KMW, Vallières E, *et al.* Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest oncology group trial S9900, an intergroup, randomized, phase III trial. *Journal of Clinical Oncology*, 2010;28(11), 1843–1849

NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet*. 2014;383(9928):1561-71

Bristol Myers Squibb. Primary non-interventional study CA2097L8: meta-analysis to characterize the association between pathological response to neoadjuvant therapy and survival endpoints in patients with stage I to III non-small cell lung cancer using patient-level data [Data on file]. 2021.

Bristol Myers Squibb. Non-interventional study CA2097C4: early endpoints in patients with resectable non-small cell lung cancer (NSCLC) in a real-world setting [Data on file]. 2021.

monitoring was a reasonable assumption. Overall, while the rationale for the adjustment in the recurrence rate seemed reasonable, the variables associated with the adjustment applied to the neoNIVO+neoChemo arm were not supported by the clinical evidence presented in the submission and, therefore, remain an area of uncertainty. Of note, a delayed cure time point in the intervention arm versus the comparator arm was recommended for both TA761 and TA823. The PSCR noted that the differential cure timepoints in the osimertinib (TA761) economic model (8 years in intervention arm and 5 years in best supportive care arm) were to account for treatment time with osimertinib (i.e., 5 years plus the 3-year maximum adjuvant osimertinib treatment time). In addition, the PSCR stated that in the atezolizumab (TA823) submission, the NICE Appraisal Committee noted that the logic in the TA761 appraisal of using an 8-year cure time point was combining a 5-year cure time point in the active monitoring group plus a 3-year osimertinib treatment period, and by the same logic, a 6-year cure time point (5-year cure time point in the active monitoring group plus a 1-year atezolizumab treatment period) was used for atezolizumab, with scenarios for 6-, 7-, and 8-year cure assumptions in the atezolizumab arm presented for transparency. The ESC acknowledged the response in the PSCR explaining the difference between the two arms (relating to the duration of therapy). The ESC noted neoNIVO was used concomitantly with neoChemo and the treatment duration of 3 cycles and considered that delaying the time point for cure for neoNIVO+neoCHEMO versus neoChemo was likely not required.

- 6.70 The submission indicated that the transition probabilities from the LR health state to the DM state could not be derived from the key trial as the trial protocol did not require monitoring for progression events following the first progression. An annual transition probability of 7.7% was calculated based on the number of patients with LR who had progressed to DM reported in a retrospective observational study²⁰ in patients with complete resection of Stage IB-IIIa NSCLC, using the median follow-up of the study. The evaluation considered that the annual transition probability estimated based on the Chouaid et al (2018) study is likely to be an underestimate, as the subjects involved in this study had a better prognosis than the CM816 population. All patients in Chouaid study had their tumour completely resected and the proportion of patients with more advanced disease (Stage III) was half that of patients in CM816 (30% vs. 64%). The transition probability from LR to DM applied in the base case (20% annually) was an estimate based on clinical expert opinion (11 oncologists). The submission did not provide any information regarding how the clinicians were selected. Therefore, the reliability and generalisability of this estimate could not be determined. In addition, the submission did not provide any evidence to support the use of an identical LR to DM transition rate between the two treatment arms and the assumption of a constant transition rate over time. The ESC agreed with the evaluation

²⁰ Chouaid C, Danson S, *et al.* Adjuvant treatment patterns and outcomes in patients with stage IB-IIIa non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. *Lung Cancer*. 2018;124:310-6.

that the use of clinical expert opinion to inform the transition probability from LR to DM was not reliable and advised that a published source should be used to inform this model input.

- 6.71 The transition probabilities from LR to death were estimated based on the KM curves of post-LR survival from CM816. A spline model (degrees of freedom = 3, hazard) was selected for extrapolation. The submission stated that none of the standard parametric distributions provided a good fit to the observed post-LR mortality data. In CM816, data on progression events following the first progression were not required to be collected according to the trial protocol. The post-LR survival data as reported in the trial reflected both the death events directly from the LR state and the death events in patients who had LR and then developed DM. The mortality of the latter population may have been double counted as the subsequent transition from DM to death has been implicitly captured by the one-off life years (LYs) applied to patients entering the DM state.
- 6.72 The health state utility values for EFS and LR were estimated based on the EQ-5D data from CM816, using Australian weights. The least square means were slightly higher in the neoNIVO+neoChemo arm than in the neoChemo arm but the difference was not statistically significant. Therefore, health state-specific utility values were applied to both treatment arms. The ESC considered this approach appropriate. It was noted in the submission that the utility for the EFS health state derived from the CM816 EQ-5D-3L data was better than the expected utility for a general Australian population with the same age range and sex distribution of CM816 as reported in the Clemens et al (2014) study²¹ (0.874 vs. 0.850). To account for this discrepancy, in the base case, the general population utility of 0.850 was used as the EFS health state utility. This implied no QoL decrements associated with a diagnosis of NSCLC and subsequent treatments, which was not realistic. Of note, the utility value for the DFS health state in the economic model for the atezolizumab PBAC submission was 0.81, which was sourced from an external study by Grutters et al 2010²². In July 2022, the PBAC noted that the utility value of 0.81 represented the median utility score in subgroups with a better QoL (e.g. patients without severe AEs and patients with Stage I disease at initial diagnosis) (Paragraph 6.48, atezolizumab PSD, July 2022 PBAC meeting). Sensitivity analyses were performed during the evaluation of the atezolizumab submission by assuming a lower DFS utility value (0.76 and 0.74, Table 16, atezolizumab PSD, July 2022 PBAC meeting). The PSCR noted the evaluator provided an alternative source for health-state utilities (Grutters et al 2010). The PSCR noted this study was based on a patient population from the Netherlands and referenced different EQ-5D population norms compared to Australia. Grutters et al 2010 referenced a population norm of 0.78 for 65 to 74 years of age, while the Australian population norm for 65 to 74 years

²¹ Clemens S, Begum N, *et al.* A comparison of EQ-5D-3L population norms in Queensland, Australia, estimated using utility value sets from Australia, the UK and USA. *Quality of Life Research*. 2014;23(8):2375-81.

²² Grutters JP, Joore MA, *et al.* Health-related quality of life in patients surviving non-small cell lung cancer. *Thorax*. 2010;65(10):903-7.

of age is 0.82 (Clemens et al 2014). The PSCR argued that the study results indicated that 'survivors of NSCLC are on average in good health' and that the average utility of non-recurrent patients (0.76) was only slightly lower than the age-matched general population utility (0.78). The ESC noted the concerns raised by the evaluation and noted that the ICER was moderately sensitive to utility values. However, the ESC considered the approach taken by the submission to account for the discrepancy in the utility for the EFS health state was likely reasonable.

- 6.73 The DM health state was modelled as an absorbing health state. When patients experienced DM, they were expected to receive a mix of therapies for first-line metastatic disease. Discounted LYs and quality-adjusted life years (QALYs) relating to these therapies were estimated based on previous PBAC submissions on treatments of metastatic NSCLC. The uncertainties surrounding the health outcomes associated with various metastatic NSCLC therapies are summarised in Table 18. Overall, the ESC agreed with the evaluation and considered that the health outcome inputs assumed in the submission were not well justified.

Table 18: Health outcome inputs for DM state

Treatment	Values	Source and comments
Health outcomes		
Pembrolizumab	LYs: 2.55 QALYs: 1.81	Pembrolizumab July 2019 PSD Table 16, PD-L1 ≥ 50%. The economic evaluation of pembrolizumab combination therapy compared with pembrolizumab monotherapy in patients with PD-L1 ≥ 50% NSCLC was based on an indirect comparison. The PBAC considered that this cost-utility analysis was not appropriate given the clinical uncertainties. The PBAC considered that, for patients with PD-L1 ≥ 50%, the PBAC recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of pembrolizumab used in combination with chemotherapy would be acceptable at the pembrolizumab price proposed in the PSCR for this population (Paragraph 7.3, Pembrolizumab PSD, July 2019 PBAC meeting). As the PBAC recommendation was not based on the cost-utility analysis as presented in the July 2019 submission, the use of estimated LYs and QALYs for pembrolizumab monotherapy in the neoNIVO+neoChemo economic model was not justified in the submission.
Pembrolizumab + PDC (non-squamous)	LYs: 2.1 QALYs: 1.57	Pembrolizumab July 2019 PSD Table 15 (PD-L1 < 50%) and Table 16 (PD-L1 ≥ 50%), weighted by outcomes stratified by PD-L1 status reported in Pembrolizumab November 2018 PSD, Table 14. As commented above, the appropriateness of the LYs and QALYs relating to pembrolizumab combination therapy in the PD-L1 ≥ 50% model has not been established. With regard to the PD-L1 < 50% model, the PBAC considered that the updates to the economic model largely addressed its major concerns with the previous model. However, the PBAC agreed with the ESC concerning the validity and appropriateness of the utilities (i.e. the application of higher utilities associated with pembrolizumab + chemotherapy, compared with chemotherapy, for both the PFS and progressive disease health states), and considered the ICER was likely to be higher than the base case presented in the resubmission (Paragraph 7.10, Pembrolizumab PSD, July 2019 PBAC meeting).
Pembrolizumab + PDC (squamous)	LYs: 1.15 QALYs: 0.84	Calculated as values of pembrolizumab + PDC (non-squamous) multiplied by ratio of squamous to non-squamous in UK submissions for nivolumab in first-line metastatic NSCLC ^a These ratios could not be verified based on the references provided in the submission. More importantly, the LYs and QALYs for pembrolizumab combination therapy in the non-squamous NSCLC population, based on which the health outcome values in squamous NSCLC patients were calculated, were not adequately justified (see the above row).
PDC	LYs: 1.24 QALYs: 0.9	Pembrolizumab July 2019 PSD Table 15, PD-L1 < 50% LYs and QALYs were taken directly from the comparator arm of the economic model for pembrolizumab + chemotherapy versus chemotherapy in the PD-L1 < 50%, non-squamous NSCLC population, not for unselected NSCLC patients. As squamous histology and PD-L1 positive expression are poor prognostic factors in advanced stage NSCLC, the LYs and QALYs gained following chemotherapy in metastatic disease are likely to be lower than the submission's estimates.
BSC	LYs: 1.12 QALYs: 0.81	BSC set to 90% of those for PDC, as per clinical expert opinion As commented previously, the estimated LYs and QALYs associated with chemotherapy are likely to have been overestimated in the submission. In addition, it is unknown whether the clinician estimate can reflect the comparative effectiveness between chemotherapy and BSC in metastatic disease.

Source: Table 99, p153 of the submission

BSC = basic supportive care; DM = distant metastasis; ICER = incremental cost-effectiveness ratio; LY = life year; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PDC = platinum-doublet chemotherapy; PFS = progression-free survival; PSCR = Pre-Sub-Committee Response; PSD = Public Summary Document; QALY = quality-adjusted life year; UK = United Kingdom

^aOutcomes for squamous patients extracted from Table 3 of 9LA unredacted Scottish Medicines Consortium detailed advice document; outcomes for non-squamous patients extracted from Table 12 of ID1566 nivolumab ERG comments on company response to Appraisal Consolidation Document

- 6.74 The costs considered in the DM health state included costs of treatments for DM (first-line and subsequent line), disease management costs, and palliative care costs. The drug costs associated with pembrolizumab as first-line therapy in DM were derived from a cost-minimisation analysis (CMA) of nivolumab + ipilimumab + chemotherapy with pembrolizumab + chemotherapy for squamous NSCLC. The PBAC recommended the listing of nivolumab as first-line treatment of squamous NSCLC on a cost minimisation basis (Paragraph 7.1, Nivolumab + ipilimumab PSD, November 2020 PBAC meeting). The drug cost per patient per course for pembrolizumab, as part of pembrolizumab combination therapy, was calculated to be \$| for squamous NSCLC, using the effective price for pembrolizumab when the nivolumab + ipilimumab submission was evaluated. This cost was used as the drug acquisition cost for pembrolizumab in the current economic model, when used in combination with chemotherapy for squamous NSCLC and non-squamous NSCLC and as monotherapy for NSCLC of any histology type. The identical pembrolizumab treatment cost suggests that the treatment duration and, thus, the progression-free survival duration are comparable among pembrolizumab monotherapy for PD-L1 \geq 50% NSCLC, pembrolizumab combination therapy for non-squamous NSCLC and pembrolizumab combination therapy for squamous NSCLC. The evaluation considered that this was not appropriate and was inconsistent with the dissimilar survival benefits applied to these treatments (LYs: 2.55 vs. 2.1 and 1.15).
- 6.75 The above concerns with the submission's approach to determining health outcomes and costs associated with treatments in the DM setting were further corroborated by the ICER for the treatment options. If the outcomes associated with pembrolizumab combination therapy (non-squamous) and pembrolizumab combination therapy (squamous) were weighted according to the NSCLC histology distribution assumed in the financial analysis (77.6%/22.4%), the QALYs gained from first-line pembrolizumab combination therapy would be 1.406, at a cost of \$|. The ICER of pembrolizumab combination therapy would be above \$75,000/QALY gained versus chemotherapy alone and above \$100,000/QALY gained versus no active treatment, unlikely to be cost-effective. Pembrolizumab monotherapy and chemotherapy would also not be cost-effective compared with best supportive care.
- 6.76 The health outcomes and costs for various NSCLC treatments in the DM setting were weighted according to the proportion of patients receiving each treatment. The weighted costs and QALYs were applied as one-off values upon entry into the DM state. The basis on which the relative use of these therapies was determined was not specified in the submission. Essentially, the base case model assumed identical treatment distribution across pembrolizumab \pm chemotherapy, chemotherapy alone and no active treatment between the model arms in the DM state. The economic model assumed that the vast majority (70.4%) of the patients would receive immunotherapy (i.e. pembrolizumab \pm chemotherapy) for treatment of metastatic NSCLC following neoNIVO+neoChemo.

Table 19: The relative use of NSCLC therapies in the DM setting and the weighted costs and outcomes

	Pembrolizumab	Pembrolizumab + PDC (squamous)	Pembrolizumab + PDC (non-squamous)	PDC	BSC	Weighted
Distribution	28.32%	9.42%	32.62%	14.64%	15%	–
Total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$50,157	\$26,028	\$ [REDACTED]
QALYs	1.81	0.84	1.57	0.9	0.81	1.357

Source: Table 99, p153, Table 100, p153 and Table 133, p196 of the submission

BSC = best supportive care; DM = distant metastasis; PDC = platinum-doublet chemotherapy; QALY = quality-adjusted life year

6.77 The ESC agreed with the evaluation that applying cost-ineffective therapies on transition into the DM health state is not appropriate. The ESC also expressed concern with the non-standard approach taken to modelling the DM health state and considered that applying one-off discounted LYs, QALYs and costs on transition into the 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 also 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 advised that a model structure that incorporates transitions from a distant metastasis health state to death is the preferred modelling approach. The pre-PBAC response maintained that the approach taken to model the DM health state was appropriate and argued that the ‘one-off approach’ captures the life-years and costs incurred during the DM health state and was selected to avoid developing a series of additional health states in metastatic disease and track progression and survival time within the DM health state for various metastatic therapies.

6.78 Key drivers of the model are summarised in Table 20.

Table 20: Key drivers of the model

Description	Method/Value	Impact Base case: \$█ ¹ /QALY gained
Time horizon	25 years	Moderate, favoured nivolumab Using a 15-time horizon increased the ICER to \$█ ² /QALY gained.
Cure assumption in the nivolumab arm	Proportion of patients 'cured' started to increase from Year 5 and achieve a maximum of 95% at Year 7.	Moderate, favoured nivolumab Delaying time point for cure by 1-2 years increased the ICER to \$█ ² -█ ² /QALY gained.
Utilities	High values for model health states derived from the key trial: 0.850 in EFS and 0.796 in LR.	Moderate, favoured nivolumab Use of lower health state utilities based on Grutters 2010 data increased the ICER to \$█ ² /QALY gained.
Health outcomes and costs in DM	There were major uncertainties in the submission's approach to determination of the health outcomes and cost relating to various DM treatment options. In addition, the submission's assumption that a majority of patients in the neoadjuvant nivolumab arm would be retreated with immunotherapy in the DM setting is not in line with current clinical practice.	Likely moderate, favoured nivolumab Assuming different payoffs applied to patient entering the DM state between the two treatment arms, the ICER could increase to \$█ ² /QALY gained.

Source: Compiled during the evaluation, based on Section 3.9 of the submission and the sensitivity analyses performed during the evaluation
DM = distant metastasis; EFS = event-free survival; ICER = incremental cost-effectiveness ratio; LR = locoregional recurrence; QALY = quality-adjusted life year

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$35,000 to < \$45,000

6.79 Table 21 presents the results of stepped economic evaluation.

Table 21: Results of the stepped economic evaluation

	neoNIVO+neoChemo	neoChemo	Increment
Step 1: Trial-based per LY gained (time-horizon of 41.4 months^a)			
Costs	\$█	\$66,485	\$█
LYs	2.89	2.81	0.09
Incremental cost/extra LYs gained			\$ ¹
Step 2: Trial-based per QALY gained (trial data transformed to clinical outcome)			
Costs	\$█	\$66,485	\$█
QALYs	2.35	2.26	0.10
Incremental cost/extra QALYs gained			\$ ¹
Step 3: Cost per LY gained extrapolated to 25 years			
Costs	\$█	\$95,163	\$█
LYs	6.62	5.39	1.23
Incremental cost per QALY gained			\$ ²
Costs	\$█	\$95,163	\$█
QALYs	5.34	4.31	1.03
Incremental cost per QALY gained			\$ ²

Source: Table 139, p203 of the submission; the 'Results' spreadsheet in the "Attachment 7 - Nivolumab neoadjuvant NSCLC Economic Evaluation" Excel workbook

QALY = quality-adjusted life year; LY = life year; neoChemo = neoadjuvant chemotherapy; neoNIVO = neoadjuvant nivolumab

^a The time point where the last trial-based event-free survival data were available.

The redacted values correspond to the following ranges:

¹ \$255,000 to < \$355,000

² \$25,000 to < \$35,000

- 6.80 Results indicate that the differences in LYs and QALYs gained between the two treatment arms during the trial period were small (0.09 LY and 0.10 QALY). The extension of the time horizon to 25 years had a significant impact on the result. The incremental LYs gained increased substantially from 0.09 to 1.23; so did the incremental QALYs (from 0.10 to 1.03). The base case ICER was estimated to be \$25,000 to < \$35,000/QALY gained, compared with \$255,000 to < \$355,000/QALY gained in the trial-based analysis.
- 6.81 The disaggregated and aggregated base case results for health outcomes are presented in Table 22. The LYs and QALYs gained were predominantly accrued in the EFS health state, with a reduction in QALYs related to LR and DM. This is consistent with the claim that the addition of neoNIVO improves EFS and leads to a reduction in recurrence. The accumulation of LYs (undiscounted) over the model time horizon in the two treatment arms are depicted in Figure 6. The majority of the LYs gained with neoNIVO+neoChemo were accrued in the extrapolated period, particularly beyond 5 years, in line with the time point when a cure rate was applied to patients remaining in the EFS health state. As stated in paragraph 6.69, the cure assumption, especially in the neoNIVO+neoChemo arm, was not sufficiently justified.

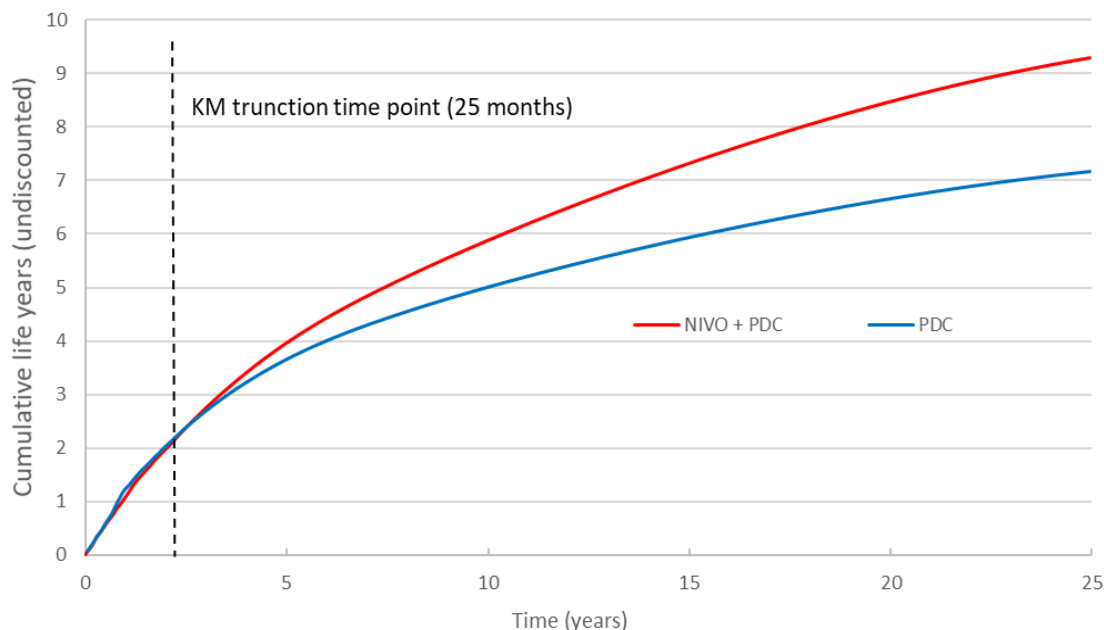
Table 22: Disaggregated summary of health outcome impacts in the economic evaluation (discounted)

	neoNIVO+neoChemo	neoChemo	Increment	% of total increment
Life years				
Event-free survival	5.43	3.85	1.58	128.7%
Locoregional recurrence	0.59	0.74	-0.14	-11.7%
Distant metastasis	0.59	0.80	-0.21	-17.0%
Total life years	6.62	5.39	1.23	100.0%
Quality-adjusted life years				
Event-free survival	4.45	3.16	1.29	125.8%
Locoregional recurrence	0.46	0.57	-0.11	-10.9%
Distant metastasis	0.43	0.58	-0.15	-14.9%
Total quality-adjusted life years	5.34	4.31	1.03	100.0%

Source: Table 141, p206 of the submission

neoChemo = neoadjuvant chemotherapy; neoNIVO = neoadjuvant nivolumab

Figure 6: Cumulative life years over the time horizon of the model (undiscounted)



Source: Constructed during the evaluation from the “Attachment 7 - Nivolumab neoadjuvant NSCLC Economic Evaluation” Excel workbook
 KM = Kaplan-Meier

Note: The disaggregated costs were driven by the neoNIVO acquisition cost (99.6% of the total incremental costs), followed by the greater medical resource use associated with disease management in the EFS health state (28.1% of the total incremental costs). The cost offsets were primarily due to the reduction in lump-sum costs in the DM health state (-26.2% of the total incremental costs).

6.82 The results of key univariate and multivariate sensitivity analyses conducted in the submission and during the evaluation are summarised in Table 23.

Table 23: Key sensitivity analyses

#	Variables altered in sensitivity analysis	Incremental costs	Incremental QALYs	ICER	% change from base case
Base case results					
		\$ [REDACTED]	1.03	\$ [REDACTED] ¹	-
Discount rate (base case = 5%)					
1a	0%	\$ [REDACTED]	1.74	\$ [REDACTED] ²	-30.20%
1b	3.5%	\$ [REDACTED]	1.19	\$ [REDACTED] ¹	-10.14%
Time horizon (base case = 25 years)					
2	15 years	\$ [REDACTED]	0.79	\$ [REDACTED] ³	21.31%
Cure assumption (base case = 5 years, 2 year linear increase to 95% cured, cured patients have general population mortality)					
3a	No cure for both arms	\$ [REDACTED]	0.81	\$ [REDACTED] ³	26.31%
3b	Onset of cure at 7 years, time from onset 2 years, 95% cured for both arms	\$ [REDACTED]	0.94	\$ [REDACTED] ³	8.87%
3c	Change the onset of cure to 6 years in the neoNIVO+neoChemo arm only ^a	\$ [REDACTED]	0.88	\$ [REDACTED] ³	16.80%
3d	Change the onset of cure to 7 years in the neoNIVO+neoChemo arm only ^a	\$ [REDACTED]	0.78	\$ [REDACTED] ³	32.81%
Source of data for time from LR to DM (base case = 20% as per clinical expert opinion)					
4	Chouaid 2018 estimate 7.7%	\$ [REDACTED]	0.98	\$ [REDACTED] ¹	4.03%
Transition from LR to death (base case = derived from the post-LR survival data in the key trial)					
5	Nil transition from LR to death ^a	\$ [REDACTED]	0.89	\$ [REDACTED] ¹	5.68%
Health state utility (base case = 0.850 in EFS and 0.796 in LR)					
6	0.76 in EFS and 0.74 in LR, based on data from Grutters et al 2010 ^a	\$ [REDACTED]	0.90	\$ [REDACTED] ³	14.35%
One-off weighted costs applied to DM (base case = \$77,065)					
7a	\$50,000 ^a	\$ [REDACTED]	1.03	\$ [REDACTED] ³	9.21%
7d	\$100,000 ^a	\$ [REDACTED]	1.03	\$ [REDACTED] ¹	-7.80%
One-off weighted QALYs applied to DM (base case = 1.357)					
8a	1.00 ^a	\$ [REDACTED]	1.07	\$ [REDACTED] ¹	-3.77%
8c	1.80 ^a	\$ [REDACTED]	0.98	\$ [REDACTED] ¹	5.10%
Criteria of retreatment with PD-(L)1 agent in the neoNIVO+neoChemo arm (base case = no restriction)					
9	Retreatment not allowed ^{a, b}	\$ [REDACTED]	0.88	\$ [REDACTED] ¹	-17.24%
Dispensed price for maximum amount (base case = public hospital DPMA, \$ [REDACTED]; private hospital DPMA, \$ [REDACTED])					
10	Published public hospital DPMA = \$7,189.57; published private hospital DPMA = \$7,330.64 (weighted nivolumab cost of \$7,283.59 per cycle) ^c	\$ [REDACTED]	1.03	\$ [REDACTED] ²	-33.76%
Multivariate analyses					
	#2 + #10 ^c	\$ [REDACTED]	0.79	\$ [REDACTED] ²	-22.58%
	#2 + #3c	\$ [REDACTED]	0.70	\$ [REDACTED] ³	38.70%
	#2 + #3c + #6	\$ [REDACTED]	0.61	\$ [REDACTED] ⁴	59.60%
	#2 + #3c + #6 + #5	\$ [REDACTED]	0.50	\$ [REDACTED] ⁵	79.89%
	#2 + #3d + #6 + #5	\$ [REDACTED]	0.47	\$ [REDACTED] ⁵	98.21%
	Assuming different QALYs and costs between the two treatment arms (neoNIVO+neoChemo vs. neoChemo) in the DM setting ^{a, d} QALYs: 0.90 vs. 1.81 Costs: \$50,157 vs. \$ [REDACTED]	\$ [REDACTED]	0.69	\$ [REDACTED] ³	13.99%

Source: Table 144, pp210-211 of the submission and sensitivity analyses performed during the evaluation

DM = distant metastasis; EFS = event-free survival; ICER = incremental cost-effectiveness ratio; LR = locoregional recurrence; neoChemo = neoadjuvant chemotherapy; neoNIVO = neoadjuvant nivolumab; PD-(L)1 = programmed cell death (ligand) 1; QALY = quality-adjusted life year

^a Additional sensitivity analyses performed during the evaluation.

^b Assuming that nil patients in the neoNIVO+neoChemo arm receive pembrolizumab therapy for metastatic disease and that the proportions of patients treated with other therapies (including chemotherapy and best supportive care) increase proportionally. This analysis was carried out by changing Cell F in the 'DM State' spreadsheet, "Attachment 7 - Nivolumab Neoadjuvant NSCLC Economic Evaluation" Excel workbook, i.e. proportion of ineligible for re-treatment of immunotherapy, into 100% (0.0% in the base case).

^c Additional sensitivity analysis performed during the development of the ESC Advice.

^d Assuming that, in the DM health state, all patients in the neoNIVO+neoChemo arm receive chemotherapy and all patients in the neoChemo arm receive pembrolizumab. The QALYs and costs associated with chemotherapy for metastatic disease were the same as the submission's estimates. The QALYs associated with pembrolizumab therapy were set to be the highest QALYs among pembrolizumab monotherapy, pembrolizumab combination therapy (non-squamous) and pembrolizumab combination therapy (squamous) and costs were set to be the lowest among the three pembrolizumab-containing therapies (refer to Table 19).

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$15,000 to < \$25,000

³ \$35,000 to < \$45,000

⁴ \$45,000 to < \$55,000

⁵ \$55,000 to < \$75,000

6.83 Results of sensitivity analyses presented in the submission and conducted during the evaluation showed that the model was most sensitive to the cure assumption, time horizon and discounting rate. Of these variables, the time horizon and cure assumptions were considered by the evaluation to be the two main economic concerns and favoured neoNIVO.

6.84 The submission assumed that the distribution of NSCLC treatments in the DM setting was the same for the two treatment arms. If this assumption holds, a change in the one-off weighted costs and QALYs would not have a large impact on the ICER (- 7.8% to +9.2% change from base case ICER across analyses), as the payoffs only applied to the absolute difference in the proportion of patients entering the DM state between the two model arms for each cycle (cumulative difference over 25 years: 11.4%). However, the submission's assumption that most patients (70.4%) in the neoNIVO+neoChemo arm would be re-treated with a PD-(L)1 inhibitor for treatment of metastatic disease is not in line with current Australian clinical practice. The evaluation noted that if such use is not allowed in the neoNIVO arm of the model, the ICER would reduce by 17%. This was attributable to the inclusion of a non-cost-effective treatment, i.e. pembrolizumab + chemotherapy and pembrolizumab monotherapy, in the neoChemo arm but not in the neoNIVO+neoChemo arm. The economic model could be more sensitive to a change in QALYs and costs associated with DM therapies in a scenario where the relative use of NSCLC therapies is different following neoNIVO+neoChemo and following neoChemo. An additional sensitivity analysis was performed by assuming that, in the DM setting, all patients in the neoNIVO+neoChemo arm receive chemotherapy and all patients in the neoChemo arm receive pembrolizumab. The QALYs and costs associated with chemotherapy for metastatic disease were sourced from the submission's estimates (i.e. 0.90 and \$50,157, respectively, Table 19). For the purpose of the sensitivity analysis, the QALYs associated with pembrolizumab therapy in the DM health state were set to be the highest QALYs among pembrolizumab monotherapy, pembrolizumab combination therapy (non-squamous) and pembrolizumab combination therapy (squamous) (i.e. 1.81, as presented in Table 19) and the costs for pembrolizumab therapy were set to

be the lowest among the three pembrolizumab-containing therapies (i.e. \$█, as presented in Table 19). Acknowledging the limitations of the assumptions, the evaluation performed this sensitivity analysis to examine whether the economic model is sensitive to the change in the DM health state payoffs. The ICER for neoNIVO+neoChemo versus neoChemo would increase to \$35,000 to < \$45,000 (14% higher than the base case result). The ESC reiterated its concerns with the non-standard approach taken to modelling the DM health state (see paragraph 6.77).

- 6.85 Results of sensitivity analyses showed that using a different jointly fitted extrapolation distribution for time to LR and for time to any progression did not affect the result greatly. However, sensitivity analyses using independent parametric functions for extrapolation could not be conducted during the evaluation, due to lack of relevant model parameters, and their impacts on the ICER are unknown. The ESC noted the additional information in the PSCR on this point, which suggests the impact of allowing independent parametric functions to be modest.
- 6.86 Other economic uncertainties, such as use of post-LR survival from the trial and transition rate from LR to DM had minimal impacts on the ICER.

Drug cost/patient/course

Table 24: Drug cost per patient for proposed and comparator drugs

	Proposed drug Trial dose and duration	Proposed drug Model	Proposed drug Financial estimates	Comparator Trial dose and duration	Comparator Model	Comparator Financial estimates
Mean dose	NIVO 360 mg Q3W + chemo Q3W ^a	NIVO 360 mg Q3W + chemo Q3W ^a	NIVO 360 mg Q3W + chemo Q3W ^a	chemo Q3W ^a	chemo Q3W ^a	chemo Q3W ^a
Mean number of 3-week cycles	2.91 ^b	2.99	NIVO: 2.91 Chemo: 2.63-2.93	2.71 ^c	2.99	2.48 - 2.86
Cost/cycle ^d	\$█	\$█	Not reported	\$418	\$418	Not reported
Cost/patient/course ^d	\$█	\$█	\$█	\$1,133	\$1,239	\$192 ^e

Source: Table constructed during the evaluation, based on Table 6.1-1, p91 of the CM816 clinical study report, Table S.4.1.1, p111 of 'CheckMate 816 Supplement tables', and 'Attachment 7 - Nivolumab neoadjuvant NSCLC Economic Evaluation' Excel workbook.

chemo = chemotherapy; NIVO = nivolumab; Q3W = every 3 weeks

^aThe 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.

^bMean 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.

^cMean 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.

^dThe submission has slightly overestimated the dispensed cost in the public hospital setting by incorrectly including dispensing fee (\$7.82). In addition, the drug prices for cisplatin, paclitaxel, and gemcitabine were not based on the most efficient vial combination. After correcting these errors, the revised cost/patient/course in the economic model would be \$█ for neoNIVO+neoChemo and \$1,163 for neoChemo.

^eThe financial analysis assumed that, without the availability of neoadjuvant nivolumab, only 12.3% of patients receive neoadjuvant chemotherapy, with the remaining 87.7% receiving adjuvant chemotherapy instead.

Estimated PBS usage & financial implications

- 6.87 This submission was not considered by DUSC. The financial analysis took an epidemiological approach to estimate the financial impacts of the proposed listing of

nivolumab plus chemotherapy for the neoadjuvant treatment of patients with resectable NSCLC. The key inputs in the financial analysis are summarised Table 25.

Table 25: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incidence of lung cancer	56.0 per 100,000 based on age-specific rate in 'Cancer in Australia 2021' (AIHW).	This approach is reasonable although changes in age distribution and methods of screening and/or diagnosis add uncertainty to the applicability of this estimate in the medium term. Incidence of earlier stage disease is likely to increase (see paragraphs 4.5 and 6.91).
% meeting other PBS criteria	86.6% of lung cancer is NSCLC (AIHW 2011)	Reasonable, and comparable with the estimate of 85.5% recently considered as appropriate by PBAC (Table 20, Atezolizumab PSD, July 2022)
	77.6% non-squamous, 22.4% squamous (PivOTAL study)	This was reasonable.
	83.50% Proportion of non-squamous NSCLC patients with no known EGFR/ALK (PivOTAL study)	Appeared reasonable estimate.
	Stage I: 16.32% - Stage IB: 52.57% - Stage IB with tumour size >=4cm: 16.78% Stage II: 9.13% Stage III: 15.60% -Stage IIIA: 55.55% (AIHW CDiA 2022, Provencio et al., 2019, Wright 2022)	There are uncertainties associated with the estimates of patients with ECOG PS (0-1) in Stages IB-IIIa.
	80% of patients with resectable tumours (assumption)	This appeared reasonable.
	85.17% ECOG PS 0-1 (Weighted distribution calculated by PS on WHO scale Kawaguchi et al., 2010 and stage distribution from AIHW CDiA 2022)	The proportion of NSCLC patients with ECOG performance status of 0-1 varied across studies (78.4% as reported in the VLCR to 95.6% from Adelphi Disease Specific Panel research). Thus, this financial input remains an area of uncertainty.
Uptake rate	██████% in Year 1 – 6. Based on advisory board feedback (excluding surgery alone). The response rate was 50% for the uptake of neoadjuvant nivolumab plus chemotherapy.	High uncertainty due to clinical algorithm change, and unknown growth rate of perioperative nivolumab plus chemotherapy treatment. The ESC considered that the estimated uptake rate was likely to be reasonable.

Source: Table 148, p217 of the submission

AIHW = Australian Institute of Health and Welfare; ALK = anaplastic lymphoma kinase; CDiA = Cancer Data in Australia; ECOG = Eastern Cooperative Oncology Group EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PS = performance status; RPBS = Repatriation Pharmaceutical Benefits Scheme; VLCR = Victorian Lung Cancer Registry; WHO = World Health Organization

6.88 The predicted use and financial implications associated with the proposed listing of Scenario 1 and Scenario 2 are summarised in Table 26 and Table 27, respectively.

Table 26: Estimated use and financial implications (Listing Scenario 1)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of nivolumab						
Total cost to the PBS/RPBS, excluding patient copayments	\$█ ²	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Estimated financial implications for other medicines						
Reduction in cost to the PBS/RPBS, excluding patient copayments	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴
Net financial implications						
Net cost to PBS/RPBS	\$█ ²	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Net cost to MBS	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴
Net cost to PBS/RPBS/MBS	\$█ ²	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³

Source: Calculated during the evaluation, using Excel workbook 'Attachment 8 - Nivolumab Neoadjuvant NSCLC Utilisation and Cost Model'.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$30 million to < \$40 million

³ \$40 million to < \$50 million

⁴ Net cost saving

Table 27: Estimated use and financial implications (Listing Scenario 2)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of nivolumab						
Total cost to the PBS/RPBS, excluding patient copayments	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Estimated financial implications for other medicines						
Reduction in cost to the PBS/RPBS, excluding patient copayments	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³
Net financial implications						
Net cost to PBS/RPBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Net cost to MBS	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³
Net cost to PBS/RPBS/MBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²

Source: Compiled during the evaluation, based on Table 172, p237 of the submission and Excel workbook 'Attachment 8 - Nivolumab Neoadjuvant NSCLC Utilisation and Cost Model'.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$30 million to < \$40 million

³ Net cost saving

6.89 In listing Scenario 2, the total cost to the PBS/RPBS was estimated to be \$30 million to < \$40 million in Year 6, and a total of \$200 million to < \$300 million in the first 6 years of listing.

6.90 The estimates did not include any grandfathering of patients.

6.91 The ESC noted recent MSAC support of the creation of a national lung cancer screening program (see paragraph 4.5). The ESC considered the creation of such a program may make it likely that more patients would be identified who were suitable for

neoadjuvant treatment. Consequently, fewer patients would be treated for metastatic disease. The overall effect of screening on financial implications is uncertain.

Quality Use of Medicines

- 6.92 The submission noted that the sponsor has implemented initiatives which include peer-to-peer education, established guidelines on the management of immune-related adverse reactions (irARs), national meetings in conjunction with conferences for oncologists, nursing and pharmacy in-services to sites where nivolumab is used, a Risk Management Plan (RMP) in Australia, and a range of educational materials and tools on irAEs for health care professionals and patients (such as mediband bracelets, a Patient Information Booklet, and an irAR wallet alert card for nivolumab).

Financial Management – Risk Sharing Arrangements

- 6.93 It was stated in the submission that the sponsor is willing to enter into a risk sharing arrangement (RSA). The sponsor acknowledged the major change related to the proposed introduction of a neoadjuvant immunotherapy. This represents a major change to the treatment paradigm, and so the sponsor is willing to undertake an RSA related to expenditure in this disease state, including the potential for subsidisation caps. Such an arrangement may provide additional certainty regarding the potential for leakage into other patient groups.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the Authority Required (STREAMLINED) listing of nivolumab for the neoadjuvant treatment of patients with resectable non-small cell lung cancer (NSCLC). The PBAC considered that nivolumab provided a moderate clinical benefit with an improvement in event-free survival (EFS) and immature overall survival (OS) data indicated a trend towards improvement. The PBAC considered the incremental cost-effectiveness ratio (ICER) was highly uncertain given the extent of extrapolation and issues with the model structure and some inputs. The PBAC considered that revised model inputs would be required to address these issues and that a price reduction would be required for nivolumab to be considered cost-effective in the neoadjuvant NSCLC setting. The PBAC considered that revised financial estimates should account for offsets for current use of immunotherapy, and considered it would be appropriate for nivolumab use to be included in the current risk sharing arrangement (RSA) in place for immunotherapies for NSCLC.
- 7.2 The PBAC noted the input from health care professionals and organisations which 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 considered there remains an unmet clinical need for more effective therapies for resectable lung cancer.

- 7.3 The PBAC noted that two PBS listing scenarios were proposed in the submission (see paragraph 3.4). Scenario 1 was agnostic to epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) status and Scenario 2 excluded patients with known sensitising EGFR mutations or ALK alterations. The PBAC noted that NSCLC with EGFR or ALK driver mutations have consistently shown poor responses to upfront immunotherapy and that patients with known sensitising EGFR or ALK alterations were excluded from the key CM816 trial. In view of this, the PBAC agreed with the ESC that there was inadequate evidence provided in the submission to support Scenario 1 and considered that Scenario 2 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.
- 7.4 The PBAC agreed with the ESC that restricting access based on PD-L1 status would not be appropriate (see paragraph 3.8), noting that a restriction agnostic to PD-L1 status would be in line with the pivotal clinical trial, the proposed TGA restriction and the September 2022 MSAC position statement²³.
- 7.5 The PBAC noted the submission proposed retreatment with a PD-L1 inhibitor for NSCLC and the clinical rationale provided for this approach (see paragraph 3.11) which was supported by the clinician in the sponsor hearing (see paragraph 6.1). Noting the short duration of neoadjuvant nivolumab therapy, the PBAC 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.
- 7.6 The PBAC considered that neoadjuvant chemotherapy (neoChemo) as the nominated main comparator was appropriate. The nomination of adjuvant chemotherapy (adjChemo) as a secondary comparator and adjuvant chemotherapy followed by atezolizumab (adjChemo+adjATEZO) as a supplementary comparator was also considered reasonable by the Committee.
- 7.7 The PBAC noted the primary evidence presented in the submission was based on a direct randomised open-label trial (CM816) comparing nivolumab plus platinum-doublet chemotherapy (neoNIVO+neoChemo) with platinum-doublet chemotherapy (neoChemo), as neoadjuvant treatment for resectable early stage NSCLC. The PBAC noted that neoNIVO+neoChemo was associated with a statistically significant improvement in EFS compared with neoChemo (HR = 0.63; 97.38% confidence interval [CI]: 0.43, 0.91) at the pre-specified Interim analysis 1. The PBAC noted the PD-L1 subgroup analyses indicated the relative reduction in hazard of an EFS event for neoNIVO+neoChemo appeared larger for tumours that express PD-L1 (see paragraph

²³ Medical Services Advisory Committee. (2022) MSAC Position Statement on programmed death-ligand 1 (PD-L1) immunohistochemistry testing to determine eligibility for treatment with PD-(L)1 checkpoint inhibitors. MSAC Position Statement - PD-L1 testing - Ratified -26Sept - clean.pdf

- 6.24) but considered that restricting access based on PD-L1 status would not be appropriate. The PBAC also noted that the magnitude of relative EFS benefit associated with neoNIVO+neoChemo over neoChemo appeared more pronounced in patients with Stage IIIA disease (N=228, HR 0.54; 95% CI: 0.37, 0.80), compared to those with earlier Stage IB/II disease (N=127, HR 0.87; 95% CI: 0.48, 1.56) but considered that due to a small sample size these results remain inconclusive.
- 7.8 Acknowledging the interim OS data were immature the PBAC noted the results indicated a trend to improved survival favouring neoNIVO+neoChemo over neoChemo (HR for death=0.57; 99.67% CI: 0.30, 1.07). The PBAC also noted that neoNIVO+neoChemo arm was associated with a reduction in the hazard of distant metastases or death compared to the neoChemo arm (HR=0.53; 95% CI: 0.36, 0.77) and agreed with the ESC that this was clinically meaningful for this patient group. Overall, the PBAC considered 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.
- 7.9 The PBAC noted that the addition of nivolumab to neoadjuvant chemotherapy did not impact on patient quality of life (QoL) compared to the use of chemotherapy alone. The Committee also noted that no detrimental effects on the proportion of patients undergoing surgery or complications were evident from the data presented.
- 7.10 The PBAC noted the rates of any adverse effects (AE) (all cause), AE of Grade ≥ 3 , and AEs resulting in treatment discontinuation (all-cause or treatment-related), were similar between the treatment arms of CM816. However, the PBAC considered the addition of nivolumab to chemotherapy was associated with an increased risk of immune checkpoint-related AEs. As such, the PBAC considered that the claim of non-inferior safety was not supported by the clinical evidence provided in the submission.
- 7.11 The PBAC considered there were major transitivity issues with the indirect treatment comparisons (ITC) of neoNIVO+neoChemo versus adjChemo and versus adjChemo+adjATEZO as a result of important unadjusted differences in study, patient, and disease characteristics. The multi-step ITC between neoNIVO+neoChemo and adjChemo+adjATEZO involved substantial modelling or adjustment of the observed data. As such, the PBAC considered that the indirect estimates of effect are unlikely to be an accurate reflection of the comparative effectiveness between the neoadjuvant use of nivolumab and the adjuvant use of atezolizumab. The PBAC considered that the ITC limitations lead to a high level of uncertainty regarding the magnitude of any incremental benefit associated with neoNIVO+neoChemo compared with either adjChemo or adjChemo+adjATEZO. As such, the PBAC considered the comparative effectiveness and safety claims compared to adjChemo and adjChemo+adjATEZO were not adequately supported by the data provided in the submission (see paragraphs 6.62 and 6.63).
- 7.12 The economic evaluation compared the health outcomes and the costs of neoNIVO+neoChemo versus neoChemo. The PBAC noted the ITCs of

neoNIVO+neoChemo versus adjChemo or adjChemo+adjATEZO were not used in the economic analysis.

- 7.13 Overall the PBAC considered the model results to be highly uncertain and likely optimistic. The PBAC noted that the incremental life years (LYs) and quality-adjusted life years (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 (see paragraph 6.68), assumptions regarding cure time points (see paragraph 6.69) and modelling the distant metastasis (DM) health state as an absorbing state in which cost-ineffective therapies were applied (see paragraphs 6.73 to 6.77).
- 7.14 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 the 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. The PBAC noted however 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.
- 7.15 The PBAC noted that 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. The PBAC considered the cure assumption variables were not well justified in the submission, especially for the neoNIVO+neoChemo arm, and potentially favoured the intervention (see paragraph 6.69). Although the ESC considered delaying the time point for cure for neoNIVO+neoCHEMO versus neoChemo was likely not required, 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.
- 7.16 The PBAC noted 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 as the EFS health state utility in the economic model. This resulted in no QoL decrements associated with a diagnosis of NSCLC or its treatment being assumed in the economic model. The PBAC noted that the ESC considered the approach taken by the submission to account for the discrepancy in the utility was likely reasonable, however considered a decrement in QoL should be modelled and therefore that the use of EFS and locoregional recurrence (LR) health-state utilities from Grutters et al 2010 would be more clinically appropriate despite its limitations.
- 7.17 The PBAC noted the economic model assumed that patients would receive immunotherapy for treatment of metastatic NSCLC following neoNIVO+neoChemo.

The PBAC considered retreatment with a PD-L1 clinically appropriate, although noted that the costs and outcomes applied for treatments in the metastatic health state did not appear to be accurate and that there was a lack of trial evidence to support retreatment.

- 7.18 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 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.
- 7.19 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 noted recent MSAC support for the creation of a national lung cancer screening program (see paragraph 4.5) 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 this stage. 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; and anticipated as a result that there would be only a small increase in expenditure for immunotherapies for NSCLC.
- 7.20 The PBAC considered that it would be appropriate for nivolumab for the proposed population to be included in the current 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.
- 7.21 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for neoadjuvant nivolumab using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- A proposed listing that excludes patients with known sensitising EGFR mutations or ALK alterations as outlined in paragraph 7.3.

- 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 that incorporates a price reduction that results in an ICER of not more than \$30,000 per QALY gained (see paragraphs 7.14 to 7.18).
- Revision of the financials to include offsets as outlined in paragraph 7.19 and recalculation of the financial implications using the revised neoadjuvant nivolumab price.
- Proposed parameters for revising the current RSA in place for immunotherapies for NSCLC to include neoadjuvant nivolumab (see paragraph 7.20).

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.22 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 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.

9 Sponsor's Comment

Bristol-Myers Squibb Australia looks forward to continuing to work with the PBAC and the Department of Health and Aged Care to provide access to nivolumab for the neoadjuvant treatment of patients with resectable non-small cell lung cancer.