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.

Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy), Authority Required (STREAMLINED) listing for the perioperative treatment of patients with resectable non-small cell lung cancer (NSCLC).

1.2 Listing of perioperative nivolumab (periNIVO) was requested by the submission on the basis of a cost-utility analysis versus neoadjuvant chemotherapy (neoChemo). Nominated secondary comparators were neoadjuvant nivolumab plus chemotherapy (neoNIVO) and adjuvant chemotherapy (adjChemo). Further, a supplementary comparator of adjChemo followed by atezolizumab was nominated as a supplementary comparator in patients with resected stage II-IIIA NSCLC whose tumours have programmed death ligand 1 (PD-L1) ≥50%. Only the comparison with neoChemo was captured in the economic analysis and financial estimates in the submission. The Pre-Sub-Committee Response (PSCR) noted that neoadjuvant nivolumab (neoNIVO) was recommended by the PBAC in July 2023 and listed on the PBS 1 August 2024 and therefore considered that it would be the therapy most likely to be replaced by periNIVO. The PSCR stated that neoNIVO was now the most appropriate main comparator and requested the listing of periNIVO be considered on the basis of a cost-minimisation approach versus neoNIVO.

1.3 The submission additionally identified two near-market comparators: perioperative pembrolizumab; and perioperative durvalumab; both of which were noted by the submission as having been submitted to the TGA for registration.

1.4 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 ≥4 cm or node positive) NSCLC
Intervention	Nivolumab 360 mg plus platinum-doublet chemotherapy Q3W for up to 4 cycles as neoadjuvant therapy Plus Nivolumab 480 mg Q4W (or 240 mg Q2W, or 3mg/kg Q2W) for up to one year as adjuvant therapy
Comparators	Main: • Neoadjuvant platinum-doublet chemotherapy Q3W for up to 4 cycles Secondary: • Nivolumab (360mg) plus platinum-doublet chemotherapy Q3W for up to 3 cycles as neoadjuvant therapy. Due to the listing of this regimen on the 1 August 2024 the PSCR changed the nominated main comparator to this regimen. • Adjuvant chemotherapy (carboplatin AUC 6 plus paclitaxel 200mg/m^2 Q3W for up to 3 cycles) Supplementary • Adjuvant chemotherapy followed by 1,200 mg atezolizumab IV Q3W for up to 16 cycles (or 1 year), or until disease recurrence [a] Near market: • Perioperative pembrolizumab: pembrolizumab (200mg) plus cisplatin-based chemotherapy Q3W for 4 cycles as neoadjuvant therapy before surgery, followed by pembrolizumab (200mg) Q3W for up to 13 cycles • Perioperative durvalumab: durvalumab (1,500mg) plus platinum-based chemotherapy Q3W for 4 cycles as neoadjuvant therapy before surgery, followed by durvalumab (1,500mg) Q4W for up to 12 cycles
Outcomes	EFS, pCR, MPR, Safety, ORR, TTDM, HRQoL
Clinical claim/s	Compared to: • neoadjuvant nivolumab plus chemotherapy (identified as main comparator in PSCR), perioperative nivolumab offers at least noninferior, and potentially superior, efficacy and noninferior safety. • neoadjuvant chemotherapy, perioperative nivolumab offers superior efficacy and noninferior safety. • adjuvant chemotherapy, perioperative nivolumab offers superior efficacy and noninferior safety • adjuvant chemotherapy followed by atezolizumab, perioperative nivolumab offers at least noninferior and potentially superior efficacy and different and overall noninferior safety • perioperative pembrolizumab, perioperative nivolumab offers noninferior efficacy and different and overall noninferior safety. • perioperative durvalumab, perioperative nivolumab offers noninferior efficacy and different and overall noninferior safety.

Source: Table 2, pp 20-21; Appendix 1, pp24-26 of the submission; PSCR (p1)
AUC = area under the curve; EFS = event-free survival; HRQoL = health-related quality of life; MPR = major pathologic response; NSCLC = non-small cell lung cancer; ORR = objective response rate; pCR = pathologic complete response; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; TTDM = time to death or distant metastases
[a] only in patients with resected stage II-IIIA NSCLC whose tumours have programmed death ligand 1 (PD-L1) ≥50%.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the Delegate's Overview was available. The Delegate was inclined to approve the registration of the following indication:

"Nivolumab, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable (tumours ≥4cm or node

positive) non-small cell lung cancer and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by nivolumab as a single agent in the adjuvant setting after surgical resection."

2.2 Conditions of registration were the submission of the dataset and final report for, the ongoing clinical trial, CM77T, and analysis of the final overall survival (OS), once the required 174 events for the OS endpoint occurred, to further characterise the clinical benefit of nivolumab in this setting.

2.3 Nivolumab, in combination with platinum-doublet chemotherapy, is currently TGA approved for neoadjuvant treatment of resectable NSCLC. neoNIVO received a positive recommendation by the PBAC at the July 2023 PBAC meeting and was PBS-listed on 1 August 2024.

2.4 Nivolumab is also currently TGA-approved as a treatment for several other types of cancer, including resectable/resected melanoma, urothelial carcinoma, oesophageal cancer and gastro-oesophageal junction cancer.

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

3 Requested listing

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	№.of Rpts
Nivolumab (initial)	Published Price $[redacted] (public) $[redacted] (private) Effective Price (submission) [a] $[redacted] (public) $[redacted] (private) Effective Price (PSCR) $[redacted] (public) $[redacted] (private)	360mg	3
Nivolumab (continuing)	Published Price $[redacted] (public) $[redacted] (private) Effective Price (submission) [a] $[redacted] (public) $[redacted] (private) Effective Price (PSCR) $[redacted] (public) $[redacted] (private)	480mg	6
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			
Proposed restriction			
Category / Program: Section 100 – Efficient Funding of Chemotherapy}			
Restriction type: ☒Authority Required (STREAMLINED)			
Indication: Resectable non-small cell lung cancer (NSCLC)			
Treatment Phase: Initial (neoadjuvant) treatment			

Clinical criteria: The condition must be at least one of: (i) node positive, (ii) at least 4 cm in size, AND The treatment must be for neoadjuvant use in a patient preparing for surgical resection, AND Patient must have a WHO performance status of 0 or 1, AND The treatment must be in combination with platinum-based chemotherapy.
Treatment criteria: Patient may receive up to a maximum of 4 PBS-subsidised doses of this drug for initial (neoadjuvant) treatment.
Prescribing Instructions: In non-squamous type NSCLC where any of the following is known to be present, this drug must not be a PBS-benefit: (i) activating epidermal growth factor receptor (EGFR) gene mutation, (ii) anaplastic lymphoma kinase (ALK) gene rearrangement.
Administrative Advice: No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
Treatment Phase: Continuing (adjuvant) treatment
Clinical criteria: The condition must have been treated with neoadjuvant nivolumab plus platinum-based chemotherapy, AND The treatment must be for the purposes of adjuvant use following surgical resection.
Treatment criteria: Patient must not be undergoing PBS-subsidised treatment with this drug where this prescription extends treatment beyond whichever comes first: (i) 12 months of adjuvant treatment, (ii) disease progression/recurrence despite treatment with this drug; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.
Administrative Advice: Up to an additional 6 repeat prescriptions (12 in total) may be sought only where dosing is on a 2-weekly schedule during adjuvant treatment. This listing's stated number of repeat prescriptions is based on 4-weekly dosing during adjuvant treatment. Special Pricing Arrangements apply.

Source: Tables 13 -15, p38 and pp41-42 of the submission

Note: The submission incorporated the following fees into the dispensed prices for nivolumab: public dispensing fees – preparation fee ($90.13); private dispensing fees –preparation fee ($90.13), diluent fee ($5.95), distribution fee ($30.05) and ready prepared dispensing fee ($8.67). These fees were updated during the evaluation. A flat 1.4% mark-up applied in the private hospital setting.

[a] The effective prices were updated during the evaluation to the current values (August 2024). Original effective prices in the submission were (480mg): $[redacted] (initial public), $[redacted] (initial private), $[redacted] (continuing public), $[redacted] (continuing private).

Text in italics indicate values calculated during evaluation.

3.1 The submission proposed a special pricing arrangement (SPA) for periNIVO, with the proposed published and effective approved ex-manufacturer price (AEMP) per 40 mg vial as $[redacted] and $[redacted] respectively, and per 100 mg vial as $[redacted] and $[redacted] respectively. The PSCR proposed a lower effective AEMP of $[redacted] and $[redacted] per 100 mg and 40 mg vial of nivolumab respectively. The requested effective AEMP is lower than the $[redacted] and $[redacted] per 100 mg and 40 mg vial accepted in the July 2023 resubmission for neoNIVO (paragraph 3.2, nivolumab Public Summary Document (PSD), July 2023 PBAC meeting).

3.2 The requested initial treatment restriction was identical to the July 2023 resubmission for neoNIVO, with the exception of the increase in maximum doses from three to four, which was consistent with the respective clinical trials, and the wording of the treatment criterion: "doses of this drug per lifetime for this indication" was altered to "doses of this drug for initial (neoadjuvant) treatment" which would allow for the addition of adjuvant doses.

3.3 For the continuing (adjuvant) treatment phase, the dose regimen of NIVO in the CM77T trial was 480 mg every four weeks (Q4W) for a maximum of 13 cycles.

Additional adjuvant dosing options of 3 mg/kg and 240 mg every two weeks (Q2W) was included in the 'Dose and Method of Administration' section of the draft product information (PI), with administrative advice added in the requested restriction to allow for additional repeat prescriptions to allow dosing on a two-weekly schedule during adjuvant treatment. The PBAC considered this was reasonable as it had previously recommended two flat dosing regimens (240 mg Q2W and 480 mg Q4W) in addition to 3 mg/kg Q2W for all existing and future PBS indications where NIVO monotherapy is used (paragraph 5.1, nivolumab PSD, March 2019).

3.4 The submission noted that the sponsor is considering opening an access program allowing eligible NSCLC patients to receive periNIVO. The submission stated that the requested restriction would allow for grandfathered patients who may have accessed treatment through the access program to be eligible for PBS treatment, and that key eligibility criteria applied as part of this access program will align with the requested restriction. Grandfathered patients were not considered in the submission's financial estimates.

3.5 The PSCR noted that the circumstances under which prescribers would choose 3 neoadjuvant doses over 4 neoadjuvant doses for their patient would be at the discretion of the prescriber and likely influenced by experience derived from immunotherapy (IO) treatment, clinician interpretation of the CM77T and CM816 trial data, and/or timing of planned surgery. The PSCR stated it would be amenable to combining the neoadjuvant portion of the restriction for the current neoadjuvant listing (3 doses) and the proposed initial restriction (4 doses) for periNIVO. The PBAC agreed with the ESC that a single restriction for neoadjuvant treatment would be reasonable (noting that a single vial price would be required).

4 Population and disease

4.1 Lung cancer is a common form of cancer in Australia with 14,782 incident cases reported in 2023 (7,696 males and 7,086 females) (AIHW, 2023). Based on an estimated 86.6% of all lung cancers being NSCLC[1] this equates to 12,801 incident cases of NSCLC in 2023. 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.

4.2 Generally, patients with Stage I-IIIB 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 and location, pulmonary and cardiac function, and the patient's willingness to undergo surgery.

[1] Table 2, PD-(L)1 checkpoint inhibitor stakeholder meeting, 8th February 2019, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-stakeholder-meetings/pdl1-stakeholder-%20meeting-outcome-statement.pdf

4.3 periNIVO is proposed to be used as an alternative to neoNIVO (main comparator proposed in the PSCR). In the case that periNIVO is listed separately on the PBS there would be two neoadjuvant NIVO regimens: every three weeks (Q3W) for a maximum of three cycles (neoNIVO listing) and Q3W for a maximum of four cycles (periNIVO listing). The PSCR noted that allowing patients to receive either 3 or 4 doses of neoadjuvant therapy followed by adjuvant therapy aligned with the draft PI.

4.4 Nivolumab is a fully human immunoglobulin G4 monoclonal antibody which binds to the 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 Epidermal Growth Factor Receptor (*EGFR*) and Anaplastic Lymphoma Kinase (*ALK*) mutations are two of the most common targetable driver mutations in NSCLC, representing distinct molecular subtypes with targeted therapeutic implications. Molecular testing for driver mutations like *EGFR* and *ALK* is crucial in non-squamous NSCLC to guide targeted therapy, whereas such mutations are rare in squamous cell carcinoma. The submission's requested PBS restriction excludes patients with known *EGFR* and *ALK* mutations in the non-squamous histology, consistent with the previous neoNIVO restriction.

4.6 At the Medical Services Advisory Committee (MSAC) November 2021 meeting, MSAC supported amendments to MBS items 73337, 73341, 73344 and 73437 to enable Medicare benefits to be payable for biomarker testing, with the term 'immunotherapy' replacing 'pembrolizumab' to cover multiple types of therapy. MBS items 73337, 73341 and 73344 allow for *EGFR*, *ALK* or *ROS1* gene status testing, respectively, for patients with NSCLC which is of non-squamous histology or histology not otherwise specified.

4.7 The PBS population proposed by the submission are unselected in terms of PD-L1 status. The PBAC has previously considered PD-L1 status in the context of the March and July 2023 neoNIVO submission. The PBAC noted that PD-L1 subgroup analyses indicated the relative reduction in hazard of an EFS event for neoNIVO appeared larger for tumours that express PD-L1 but considered that restricting access based on PD-L1 status would not be appropriate (paragraph 7.7, nivolumab PSD, March 2023 PBAC meeting).

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 2. Due to the listing of neoadjuvant nivolumab (1 August 2024) the PSCR changed the nominated main comparator to be: nivolumab (360mg) plus platinum-doublet chemotherapy for up to 3 cycles as neoadjuvant therapy.

Table 2: Comparators nominated in the submission and rationale described in the submission

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 perioperative nivolumab 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 followed by nivolumab as an adjuvant treatment.
Resectable (tumours ≥4 cm or node positive) NSCLC	Secondary	Adjuvant chemotherapy	The comparator treatment is currently available on the PBS. Based on the results of the CM77T trial presented in the submission, it is likely that some clinicians would substitute adjuvant chemotherapy for perioperative nivolumab.
Resectable (tumours ≥4 cm or node positive) NSCLC	Secondary	Neoadjuvant nivolumab + chemotherapy	The comparator treatment has been recommended by the PBAC and was PBS-listed on 1 August 2024. It is likely that some clinicians would substitute neoadjuvant nivolumab plus chemotherapy for perioperative nivolumab.
Resectable stage IIA-IIIB (N2) NSCLC	Near market comparator	Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab	It is likely that some clinicians would substitute perioperative pembrolizumab for perioperative nivolumab.
Resectable stage IIA-IIIB (N2) NSCLC	Near market comparator	Neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab	It is likely that some clinicians would substitute perioperative durvalumab for perioperative nivolumab.
Resected stage II-IIIA NSCLC whose tumours have PD-L1 ≥50%	Supplementary comparator	Adjuvant chemotherapy, followed by atezolizumab	Atezolizumab is the only immunotherapy currently PBS listed for resectable/resected NSCLC.

Source: Table 7, pp28-29 of the submission.
Abbreviations: NSCLC = non-small cell lung cancer; PD-L1 = Programmed death-ligand 1

5.2 The ESC agreed with the PSCR that given the recent PBS listing of neoNIVO, that it would be the therapy most likely to be replaced by periNIVO, making it the most appropriate main comparator.

5.3 The submission presented an economic evaluation for the comparison of periNIVO versus neoChemo in adult patients with resectable (tumours ≥4 cm or node positive) NSCLC. The PSCR presented a cost-minimisation for the comparison of periNIVO versus neoNIVO.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from an individual and organisations (3) via the Consumer Comments facility on the PBS website. An individual accessing nivolumab through a clinical trial stated that there were limited treatment options for their type of lung cancer and expressed concern of exhausting treatment options. The individual noted that the condition has had a profound impact on their and their family member's mental health and quality of life. The individual highlighted that the side effects associated with nivolumab had led to multiple hospitalisations, which significantly affected their physical and emotional well-being. Concerns were also raised about the affordability of medications without PBS reimbursement.

6.3 The PBAC acknowledged the input from Rare Cancers Australia and Lung Foundation Australia expressing their support for the listing of nivolumab for the perioperative treatment of resectable NSCLC. The organisations emphasised the importance of additional treatment options for this patient group and considered that nivolumab as perioperative treatment could result in considerable benefits for NSCLC patients and their carers and families. Rare Cancers Australia noted the side effects associated with currently available treatment options for NSCLC, that significantly impacted patients' physical well-being and quality of life. Rare Cancers Australia emphasised the high emotional and financial burden associated with this condition. Rare Cancers Australia also noted the side effects experienced by patients receiving nivolumab included muscle cramps, weight gain, feeling cold, dry skin and hair changes – however noted that patients most often reported that these side effects were manageable and did not outweigh the potential benefits of treatment.

6.4 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 CM77T trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for periNIVO versus neoChemo, 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 therapies.[2]

Clinical trials

6.5 The submission's primary evidence was based on a direct randomised, double-blind trial (CheckMate77T; CM77T) comparing periNIVO (360 mg NIVO intravenous [IV] Q3W for a maximum of four cycles plus platinum-doublet chemotherapy, followed by surgery, followed by 480 mg IV NIVO Q4W for a maximum of 13 cycles) with

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

neoChemo (neoadjuvant platinum-doublet Q3W for a maximum of four cycles, followed by surgery), for resectable NSCLC (Stage IIA [>4cm] to IIIB [N2]; American Joint Commission on Cancer [AJCC], 8th Edition).

6.6 For the main comparator proposed in the PSCR, neoNIVO, the submission's evidence was based on an adjusted (Bucher method) indirect treatment comparison (ITC) of periNIVO in CM77T with neoNIVO in CM816, using neoChemo as common reference. The randomised open-label trial CM816 compared neoNIVO (360 mg nivolumab IV Q3W for a maximum of three cycles plus platinum-doublet chemotherapy) with neoChemo (platinum-doublet chemotherapy for a maximum of three cycles) as neoadjuvant treatment for resectable early stage NSCLC (Stage IB (≥ 4 cm) – IIIA, American Joint Commission on Cancer (AJCC), 7th Edition).

6.7 For the secondary comparator adjChemo, the submission's evidence was based on an adjusted multistep ITC (Bucher method) between periNIVO in CM77T with adjChemo in the NATCH trial, using neoChemo and surgery as the common reference. The three-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). 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.

6.8 Comparisons between periNIVO and the supplementary comparator atezolizumab and the near market comparators perioperative pembrolizumab and perioperative durvalumab were presented in an appendix to the submission. Although atezolizumab was considered as offsets in the financial estimates, these comparisons were not considered in the economic evaluation.

6.9 The comparisons outlined in paragraphs 6.7 and 6.8 will not be discussed further in this document.

6.10 Key details of the CM77T and CM816 trials as presented in the submission are provided in Table 3. The PBAC has previously considered results from CM816 in the consideration of neoNIVO in NSCLC at the March 2023 and July 2023 PBAC meetings.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct comparison between periNIVO and neoChemo		
CM77T NCT04025879	Phase 3, Randomized, Double-Blind Study Of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy Plus Placebo, Followed By Surgical Resection And Adjuvant Treatment With Nivolumab Or Placebo For Participants With Resectable Stage II-IIIb Non-Small Cell Lung Cancer (Checkmate 77T)	Clinical study report 10 November 2023
	Cascone, T., Awad, M.M., Spicer, J.D., He, J., Lu, S., Sepesi, B., Tanaka, F., Taube, J.M., Cornelissen, R., Havel, L. and Karaseva, N., 2024. Perioperative Nivolumab in Resectable Lung Cancer	*N Engl J Med* 2024; 390: 1756-1769
	Cascone, T., et al. "LBA1 CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II-IIIb NSCLC."	Conference abstract *Annals of Oncology* 2023, 34(S2):S1295
Trials used for indirect comparisons with periNIVO from CM77T		
CM816 NCT0998528	Randomized, open-label, Phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early stage NSCLC: Report date 22 November 2022	Clinical study report 22 November 2022
	Forde, P. M., Spicer, J., Lu, S., et al. 2022. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer.	*N Engl J Med* 2022; 386(21): 1973-1985
	Forde, P.M., Spicer, J., Girard, N., Provencio, M., Lu, S., Wang, C., Awad, M., Mitsudomi, T., Felip, E., Swanson, S.J. and Saylors, G., 2023. 84O Neoadjuvant nivolumab (N)+ platinum-doublet chemotherapy (C) for resectable NSCLC: 3-y update from CheckMate 816.	Conference abstract *Journal of Thoracic Oncology* 2023, 18(4): S89-S90
	Spicer, J., Girard, N., Provencio, M., Lu, S., Wang, C., Awad, M., Mitsudomi, T., Felip, E., Swanson, S.J., Saylors, G., and Forde, P.M., 2024. Neoadjuvant nivolumab plus chemotherapy vs chemotherapy in patients with resectable NSCLC: 4-y update from CheckMate 816.	Conference abstract *ASCO Annual Meeting Abstract (LBA8010)*

Source: Table 22, 23, 24 and 26, pp56-60 of the submission

Note: Spicer 2024, the 4 year update of CM816 has not been previously considered by the PBAC at the neoadjuvant nivolumab March and July 2023 PBAC meetings.

6.11 The key features of the included trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
periNIVO vs neoChemo					
CM77T	461	R, DB, MC 25.4 months (IA)	Low	Resectable NSCLC Clinical Stage IIA-IIIB (AJCC 8th Edition).	EFS, pCR, MPR, ORR [a], TTDM [a], AEs
neoNIVO vs neoChemo					
CM816	358	R, OL, MC 29.5 months (1IA) 41.4 months (2IA) 57.6 months (3IA)	Low	Resectable NSCLC Clinical Stage 1B-IIIA (AJCC 7th Edition).	EFS, OS

Source: Table 29, Table 30 pp67-69 of the submission, p3140 of Felip 2010

AEs=adverse events; AJCC=American Joint Committee on Cancer; DB=double blind; DFS=disease free survival; EFS=event free survival; IA = interim analysis; LR = locoregional recurrence; MC=multi-centre; MPR=major pathological response; NSCLC=non-small cell lung cancer; OL=open label; OS=overall survival; pCR=pathological complete response; R=randomised; TTMD=time to death or metastatic disease

[a] ORR and TTDM were exploratory endpoints of CM77T

6.12 The risk of bias was considered low for the direct comparison in the CM77T trial. For the indirect treatment comparisons (ITCs), there were several transitivity issues across

the studies due to unadjusted differences in study design, patient clinical characteristics and demographics. These are discussed further in paragraph 6.45.

Comparative harms

6.13 A summary of overall adverse events (AEs) in CM77T is presented in Table 5. Frequently reported treatment-related AEs (≥15% of patients in any treatment arm) in CM77T are summarised in Table 6.

Table 5: Summary of key adverse events reported in CM77T

	periNIVO (N=228)	neoChemo (N=230)	RR (95% CI)	RD (95% CI)
Any adverse event (all-causality)	222 (97.4%)	225 (97.8%)	0.99 (0.97, 1.02), p = 0.32	-0.5 (-3.3, 2.3)
Any adverse event Grade ≥ 3 (all-causality) [a]	115 (50.4%)	103 (44.8%)	1.13 (0.93, 1.37), p = 0.23	5.7 (-3.5, 14.8)
Any SAE (all-causality)	96 (42.1%)	71 (30.9%)	**1.36 (1.07, 1.74)**	**11.2 (2.5, 20.0)**
Any SAE Grade ≥ 3-4 (all-causality)	65 (28.5%)	46 (20.0%)	**1.43 (1.02, 1.98)**	**8.5 (0.7, 16.3)**
Adverse events resulting in treatment discontinuation (all-causality)	56 (24.6%)	25 (10.9%)	**2.26 (1.46, 3.49), P = 0.0002**	**13.7 (6.8, 20.6)**
Adverse events resulting in treatment discontinuation (study drug related)	44 (19.3%)	17 (7.4%)	**2.61 (1.54, 4.43), p = 0.0004**	**11.9 (5.8, 18.0)**
Deaths due to study drug toxicity [b]	2 (0.9%)	0 (0.0%)	5.04 (0.24, 104.49), P = 0.30	0.9 (-0.3, 2.1)
Surgery related adverse events	73/178 (41.0%)	69/178 (38.8%)	1.06 (0.820, 1.37), p = 0.67	2.2 (-7.9, 12.4)
Immune-mediated adverse events				
Pneumonitis (any grade)	12 (5.3%)	3 (1.3%)	**4.04 (1.15, 14.11)**	**4.0 (0.7, 7.2)**
Grade ≥ 3	5 (2.2%)	2 (0.9%)	2.52 (0.49, 12.87)	1.3 (-0.9, 3.6)

Source: Table 73, p120 of the submission, Table 8.1.1-1, Table 8.4-1 p103, p123 of the CM77T clinical study report and compiled/calculated during the evaluation

Abbreviations: CI = confidence interval; neoChemo = neoadjuvant chemotherapy; periNIVO = perioperative nivolumab; RR = relative risk; SAE = serious adverse event

Note: Bold values indicate results where the 95% CI did not include the null.

[a] The reported number of ≥ Grade 3 (all-causality) events provided by the submission could not be verified during evaluation. Table 8.2-1, p113-4 of the CM77T CSR reported 108 (47.4%) and 99 (43.0%) grade 3-4 events for periNIVO and neoChemo respectively, compared to 115 (50.4%) and 103 (44.8%) reported by the submission.

[b] Two deaths due to study drug toxicity (per investigator) were reported in the periNIVO treatment arm. Both patients were reported to have died of pneumonitis after completing four cycles of neoadjuvant treatment.

Table 6: Frequently reported treatment-related adverse events (≥ 15% of patients in any treatment arm) – CM77T

	periNIVO (N=228)	neoChemo (N=230)	RR (95% CI)	RD (95% CI)
Any Grade Treatment-related adverse events	203 (89.0%)	200 (87.0%)	1.02 (0.96, 1.10)	2.1 (-3.9, 8.0)
Anaemia	57 (25.0%)	51 (22.2%)	1.13 (0.81, 1.57)	2.8 (-4.9, 10.6)
Nausea	53 (23.2%)	65 (28.3%)	0.82 (0.60, 1.12)	-5.0 (-13.0, 3.0)
Alopecia	52 (22.8%)	53 (23.0%)	0.99 (0.71, 1.38)	-0.2 (-7.9, 7.5)
Constipation	51 (22.4%)	39 (17.0%)	1.32 (0.91, 1.92)	5.4 (-1.9, 12.7)
Fatigue	47 (20.6%)	44 (19.1%)	1.08 (0.75, 1.56)	1.5 (-5.8, 8.8)
Decreased neutrophil count	35 (15.4%)	20 (8.7%)	**1.77 (1.05, 2.96)**	**6.7 (0.7, 12.6)**
Neutropenia	21 (9.2%)	23 (10.0%)	0.92 (0.52, 1.62)	-0.8 (-6.2, 4.6)
Grade ≥3-4 Treatment-related adverse events	74 (32.5%)	58 (25.2%)	1.29 (0.96, 1.72)	7.2 (-1.0, 15.5)
Anaemia	8 (3.5%)	8 (3.5%)	1.01 (0.39, 2.64)	0.0 (-3.3, 3.4)
Nausea	2 (0.9%)	3 (1.3%)	0.67 (0.11, 3.99)	-0.4 (-2.3, 1.5)
Alopecia	1 (0.4%)	0	-	0.4 (-0.4, 1.3)
Constipation	0	1 (0.4%)	-	-0.4 (-1.3, 0.4)
Fatigue	5 (2.2%)	2 (0.9%)	2.52 (0.49, 12.87)	1.3 (-0.9, 3.6)
Decreased neutrophil count	23 (10.1%)	15 (6.5%)	1.55 (0.83, 2.89)	3.6 (-1.5, 8.6)
Neutropenia	8 (3.5%)	13 (5.7%)	0.62 (0.26, 1.47)	-2.1 (-6.0, 1.7)

Source: Table 74, Table 77, p121 & p124 of the submission, Table 8.1.1-1 pp. 103-5 CM77T CSR and compiled/calculated during the evaluation

Abbreviations: neoChemo = neoadjuvant chemotherapy; periNIVO = perioperative nivolumab

Note:. Bold values indicate results where the 95% CI did not include the null

6.14 The rates of AE Grade ≥3 (all cause), SAEs (all cause), SAEs ≥3 (all cause) and AEs resulting in treatment discontinuation (all cause and treatment related) were higher in the periNIVO arm compared with the neoChemo arm. There were two deaths due to study drug toxicity (per investigator) reported in the periNIVO treatment arm and zero reported in the neoChemo arm. Both patients were reported to have died of pneumonitis after completing four cycles of neoadjuvant treatment.

6.15 In patients treated with periNIVO compared to patients treated with neoChemo, the most common Grade ≥3 treatment-related AEs were decreased neutrophil count (10.1% versus 6.5%), anaemia (3.5% each) and neutropenia (3.5% versus 5.7%, respectively).

6.16 The most frequently reported immune-mediated AEs (IMAEs) reported for patients treated with periNIVO were: hypothyroidism/thyroiditis (11%); pneumonitis (5%); rash (5%); and hyperthyroidism (5%). The nature of these IMAEs is consistent with the established IMAE profile of immunotherapy-based treatment regimens. See Table 8 for details.

6.17 Compared with patients treated with neoChemo, patients treated with periNIVO were observed to have had a notably higher rate of any-grade thyroiditis (11% versus 1.7%). The numerically higher incidence of pneumonitis (periNIVO: n=12 [5.3%], neoChemo: n=3 [1.3%]) may be important, given pneumonitis was attributed as the cause of death due to study drug toxicity (per investigator) for two (0.9%) patients in the periNIVO arm.

6.18 Overall, the submission's claim of noninferiority for the safety of periNIVO compared with neoChemo was not supported by the presented AE data. The rate of any SAEs (all-causality) was substantially higher in the periNIVO arm compared with neoChemo

(RD =11.2, 95%CI 2.5, 20.0), as was the rate of Grade ≥3–4 SAEs (all-causality) (RD = 8.5, 95%CI 0.7, 16.3). In addition, the rate of AEs resulting in treatment discontinuation was more than double in the periNIVO arm compared with neoChemo (RD = 13.7, 95%CI 6.8, 20.6), as was the rate of study-drug related AEs resulting in treatment discontinuation (RD = 11.9, 95%CI 5.8, 18.0).

6.19 The PBAC, in the consideration of the March 2023 neoNIVO submission, considered that a claim of noninferior safety for neoNIVO versus neoChemo was not supported by the clinical evidence (paragraph 7.10, nivolumab PSD, March 2023 PBAC meeting). This was reaffirmed in the July 2023 meeting (paragraph 5.6, nivolumab PSD, July 2023 PBAC meeting). Therefore, it would follow that periNIVO (which adds adjuvant NIVO treatment to neoNIVO) would be unlikely to have noninferior safety compared with neoChemo.

6.20 The indirect comparisons of safety between periNIVO and neoNIVO are presented in Table 7 and Table 8. There was no description of methodology for the relative risk calculations for adverse events in the ITC in the submission and it was unclear if this was an anchored or unanchored comparison. No formal statistical comparison of IMAEs were presented.

Table 7: Relative risk of adverse events in NIVO arms of CM77T (perioperative) and CM816 (neoadjuvant)

	CM77T	CM816: Interim analysis 1 [a]	CM816: 4-year update [b]	RR [c] (95%CI)
	periNIVO (N=228)	neoNIVO (N=176)	neoNIVO (N=176)	
Any adverse event (all-causality)	222 (97%)	163 (93%)	165 (94%)	1.0 (0.99, 1.1), p = 0.09
Any adverse event ≥ Grade 3 (all-causality)	**115 (50%)**	72 (41%)	76 (43%)	1.2 (0.94, 1.44), p = 0.15
Adverse events resulting in treatment discontinuation (all-causality)	**56 (25%)**	18 (10%)	19 (11%)	**2.3 (1.4, 3.9), p = 0.0008**
Adverse events resulting in treatment discontinuation (study drug-related)	**44 (19%)**	18 (10%)	19 (11%)	**1.8 (1.1, 2.9), p = 0.02**
Deaths due to study drug toxicity	2 (0.9%)	0	0	3.9 (0.19, 80.0), p = 0.38
Surgery related adverse events	73/178 (41%)	62/149 (42%)	NR	-

Source: Table 79, Table 80, pp127-128 of the submission

Abbreviations: EFS = event-free survival; neoChemo = neoadjuvant chemotherapy; neoNIVO = neoadjuvant nivolumab plus chemotherapy; periNIVO = perioperative nivolumab

[a] Median follow up of 29.5 months

[b] Median follow up of 57.6 months

[c] The relative risks presented by the submission compared CM77T interim analysis (median follow up 25.4 months) to the CM816 4-year update (median follow up 57.6 months)

Note: Cells in bold indicate values where the 95%CI did include the null, cells shaded in blue reflect information previously considered by the PBAC.

Table 8: Comparison of immune mediated adverse events: CM77T and CM816

	CM77T		CM816: Interim analysis 1 of EFS	
	periNIVO (N=228)		neoNIVO (N=176)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Rash	11 (5%)	2 (0.9%)	15 (9%)	3 (2%)
Hypersensitivity	1 (0.4%)	0	2 (1%)	0
Pneumonitis	12 (5%)	5 (2%)	2 (1%)	0
Endocrine				
Adrenal insufficiency	4 (2%)	0	2 (1%)	2 (1%)
Hypophysitis	2 (0.9%)	0	1 (0.6%)	1 (0.6%)
Hypothyroidism/thyroiditis	**25 (11%)**	0	4 (2%)	0
Hyperthyroidism	11 (5%)	1 (0.4%)	7 (4%)	0
Diabetes mellitus	2 (0.9%)	0	2 (1%)	0

Source: Table 82, p130 of the submission
EFS = event-free survival; neoNIVO = neoadjuvant nivolumab; periNIVO = perioperative nivolumab
Note: Cells in bold indicate >5% difference in events between trials. Cells shaded in blue reflect information previously considered by the PBAC.

6.21 Noting the limitations of the methodology used to compare AEs in the submission and a likely high risk of bias and uncertainty, the clinical evidence showed a higher proportion of patients treated with periNIVO in CM77T experienced any AEs (all-causality) compared with patients treated with neoNIVO in CM816 (50% versus 43%, respectively). Moreover, the proportion of patients that experienced any AEs resulting in treatment discontinuation (all-causality) in the periNIVO arm in CM77T was more than double that of the neoNIVO arm in CM816 (25% versus 10%; RR=2.3 [95%CI 1.1, 2.9: p<0.001]), and there appeared to be a high incidence of hypothyroidism/thyroiditis in patients treated with periNIVO in CM77T than patients treated with neoNIVO in CM816. Overall, the evaluation considered that the presented data did not support the safety claim that periNIVO was noninferior to neoNIVO. While it was plausible that periNIVO, which includes more doses of nivolumab compared to neoNIVO, would be associated with more AEs, a claim of inferior safety for periNIVO compared to neoNIVO was likely more appropriate.

6.22 The PBAC has previously considered that the addition of nivolumab to chemotherapy was associated with an increased risk of immune checkpoint-related AEs (paragraph 7.10, nivolumab PSD, March 2023). It therefore follows that periNIVO, which is adding further adjuvant PD-L1 treatment, would unlikely be noninferior to neoChemo.

6.23 The PSCR acknowledged that a higher proportion of AEs, including AEs resulting in treatment discontinuation, were reported in patients treated with periNIVO compared with neoNIVO. The ESC agreed with the Response that patients in the CM77T trial had a longer treatment duration compared to CM816, and therefore the increased incidence of AEs in CM77T would be expected. However, the ESC noted that this also indicated that periNIVO was inferior in terms of safety compared to neoNIVO.

Benefits/harms

6.24 A benefits and harms table is not presented for the main comparison of periNIVO with neoNIVO as the submission made a claim of noninferiority.

6.25 A summary of the comparative benefits and harms for periNIVO versus neoChemo is presented in Table 9.

Table 9: Summary of comparative benefits and harms for periNIVO and neoChemo

Benefits					
Event-free survival[a] by (median duration of follow up 25.4 months)					
Event		**periNIVO**	**neoChemo**		**HR (95% CI)**
Events, n/N (%)		76/229 (33.2)	113/232 (48.7)		0.58 (0.43, 0.78)
Median EFS duration, months (95% CI)		Not Reached (28.94, NA)	18.43 (13.63, 28.06)		-
Landmark survival estimates, probability (95% CI)					**RD**
6 months		84.6 (79.1, 88.8)	79.9 (73.8, 84.7)		4.7
12 months		73.4 (66.8, 78.9)	59.2 (52.2, 65.6)		14.2
18 months		70.2 (63.4, 76.0)	50.0 (42.9, 56.7)		20.2
Harms					
periNIVO, n/N	**neoChemo, n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
			periNIVO	**neoChemo**	
Any SAEs (all-causality)					
96/228	71/230	1.36 (1.07, 1.74)	42.1	30.9	11.2 (2.5, 20.0)
Adverse events resulting in treatment discontinuation (all-causality)					
56/228	25/230	2.26 (1.46, 3.49)	24.6	10.9	13.7 (6.8, 20.6)
Pneumonitis (any grade)					
12/228	3/230	4.04 (1.15, 14.11)	5.3	1.2	4.0 (0.7, 7.2)
Rash (any grade)					
11/228	2/230	5.55 (1.24, 24.75)	4.8	0.9	4.0 (0.9, 7.0)
Thyroiditis (any grade)					
25/228	4/230	6.30 (2.23, 17.83)	11.0	1.7	9.2 (4.8, 13.6)

Source: Compiled during evaluation using information sourced from Table 73, Table 75, p120 and p122 of the submission
Abbreviations: HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio
[a] Event-free survival was defined in the CM77T trial as the length of time from randomisation to disease progression or death from any cause. Disease progression included progression that precluded surgery, abandoned surgery owing to unresectability, progression or recurrence with or without surgery and death. Overall survival was not reported at the time of interim analysis as data was immature.

6.26 On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with periNIVO in comparison with neoChemo, after a median duration of follow-up of 25.4 months:

- Approximately 14 patients would remain event free at 12 months;
- Approximately 11 additional patients will experience any SAE;
- Approximately 14 additional patients will discontinue treatment as a result of an AE; and
- Approximately 4 additional patients will experience any grade pneumonitis, 4 additional patients will experience any grade rash, and 9 additional patients will experience any grade thyroiditis (inflammation of the thyroid gland).

Comparative effectiveness

6.27 The event-free survival[3] (EFS) results from the CM77T interim analysis (median follow-up 25.4 months) are summarised in Table 10. The EFS Kaplan-Meier (KM) curves in CM77T are presented in Figure 1.

Table 10: Event-free survival results – CM77T: BICR

	periNIVO (n=229)	neoChemo (n=232)
Interim analysis 1: median follow-up 25.4 months		
n/N with event (%)	76/229 (33.2)	113/232 (48.7)
Median time-to-event (95% CI)	NR (28.94, NR)	18.43 (13.63, 28.06)
Hazard ratio (95% CI) [a]	0.58 (0.43, 0.78)	
Hazard ratio (97.36% CI) [a]	**0.58 (0.42, 0.81), p < 0.001**	
EFS rates (95% CI) [b]		
12 months	73.4 (66.8, 78.9)	59.2 (52.2, 65.6)
18 months	70.2 (63.4, 76.0)	50.0 (42.9, 56.7)

Tables 50-51, p89 of the submission

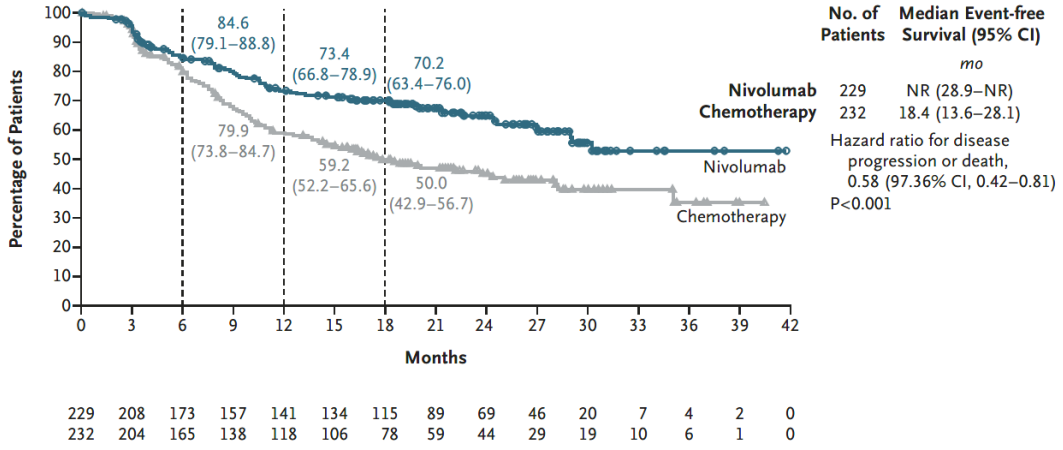
Abbreviations: BICR = blinded independent central review; CI = confidence interval; EFS = event-free survival; ITT = intention to treat; NR = not reached; neoChemo = neoadjuvant chemotherapy; periNIVO = perioperative nivolumab

[a] Stratified Cox proportional hazard model, the p-value threshold for statistical significance was 0.0264

[b] Based on Kaplan-Meier estimates

Note: Bolded cells represent statistically significant results.

Figure 1: Kaplan-Meier curve for EFS by BICR – CM77T



Source: Figure 12, p90 of the submission

Abbreviations: BICR = blinded independent central review; CI = confidence interval; NR = not reached

6.28 The submission nominated a minimal clinically important difference (MCID) of 0.85 for EFS, such that if the EFS hazard ratio (HR) for periNIVO compared with comparator treatments is ≤0.85 then the improvement in disease progression/recurrence was deemed clinically important. The nominated MCID was based on a meta-analysis of 15 randomised controlled trials[4] which reported a HR for recurrence free survival for the

[3] EFS by blinded independent central review (BICR) was a composite endpoint defined as time from randomisation to any event of progression of disease or worsening of disease precluding surgery, if surgery was attempted but gross resection was abandoned due to unresectable tumour or worsening of disease, progression or recurrence of disease after surgery, progression or recurrence of disease without surgery, or death due to any cause.

[4] NSCLC Meta-analyses 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

use of neoChemo compared with surgery alone of 0.85 (95% confidence interval [CI]: 0.76, 0.94, p = 0.002). It is unclear whether the submission's nominated MCID for EFS (HR ≤0.85) is an appropriate MCID. No noninferiority margin was nominated in the submission.

6.29 Based on the prespecified CM77T interim analysis 1 of EFS, periNIVO was associated with a statistically significant improvement in EFS compared with neoChemo (EFS HR = 0.58 [97.36% CI 0.42, 0.81]: stratified log-rank test p-value < 0.001). The median EFS should be interpreted with caution as the number of events had not reached 50% in either treatment arm. The p-value threshold for statistical significance (p=0.0264) was crossed and the observed HR was lower than the submission's nominated MCID of ≤0.85.

6.30 There were 76/229 (33.2%) EFS events in the periNIVO arm and 113/232 (48.7%) events in the neoChemo arm. The most common type of event in the periNIVO and neoChemo arms was progression/recurrence after surgery (47.4% [36/76] and 68.1% [77/113] respectively). Deaths accounted for 22.4% (17/76) of EFS events in the periNIVO arm, and 7.1% (8/113) of events in the neoChemo arm.

6.31 The KM plot showed a similar EFS between the two treatment arms over the first three months, after which the curves begin to diverge. The percentage of patients alive and without disease progression or disease recurrence was higher in the periNIVO arm than in the neoChemo arm at 12 months (point estimates: 73.4% vs 59.2%), and at 18 months (point estimates: 70.2% vs 50.0%), representing a 14.2% and 20.2% difference in favour of patients enrolled in the periNIVO arm at 12 and 18 months, respectively.

6.32 Overall survival, which was a secondary outcome of CM77T, was not analysed at the interim analyses as the data remained immature and follow up ongoing. Instead, OS data from CM816 was presented (Table 11), with the corresponding KM curve in Figure 2. The PBAC has previously considered OS results from CM816 at the July 2023 PBAC meeting, for the 3-year update (median follow-up 41.4 months). In this submission, data from a more recent 4-year update (median follow-up 57.6 months) of CM816 was available.

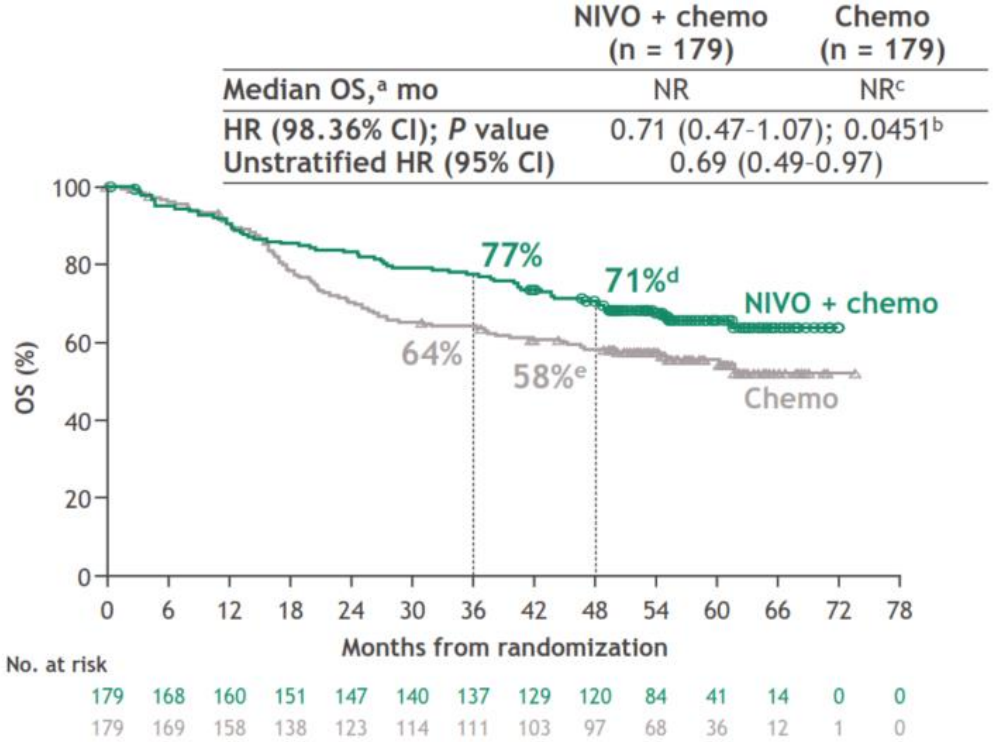
6.33 Based on the most recent CM816 4-year update of OS (data cutoff 23 February 2024, median follow-up 57.6 months) there was a trend in favour of neoNIVO arm compared to neoChemo (HR = 0.71 [95% CI 0.47, 1.07]: p=0.0451). The stopping boundary for declaring statistical significance (0.0164) was not crossed and therefore statistically significant differences could not be claimed. Median OS was still yet to be reached in either treatment arm of CM816.

Table 11: Overall survival results – CM816

	neoNIVO	neoChemo
Interim analysis 1: median follow-up 29.5 months		
n/N with event (%) [a]	NA/179	NA/179
Median time-to-event (95% CI)	NA (NA, NA)	NA (NA, NA)
Hazard ratio [e]	0.57 (99.67% CI: 0.30, 1.07), p = 0.008 [b]	
3-year update: median follow-up 41.4 months		
n/N with event (%) [a]	NA/179	NA/179
Median time-to-event (95% CI)	NA (NA, NA)	NA (46.8, NA)
Hazard ratio [e]	0.62 (99.34% CI: 0.36, 1.05), p = 0.0124 [c]	
4-year update: median follow-up 57.6 months		
n/N with event (%) [a]	NA/179	NA/179
Median time-to-event (95% CI)	NA (NA, NA)	NA (50.4, NA)
Hazard ratio [e]	0.71 (98.36% CI: 0.47, 1.07), p = 0.0451 [d]	

Tables 66, p110 of the submission, Slide 6 of Spicer 2024 ASCO presentation
Abbreviations: CI = confidence interval; ITT = intention to treat; neoNIVO= neoadjuvant nivolumab plus chemotherapy; NA = not available/not reached; neoChemo = neoadjuvant chemotherapy; NR = not reported
[a] Number of events were not reported
[b] The stopping boundary for statistical significance (0.0033) was not crossed at this first interim analysis
[c] The stopping boundary for statistical significance (not reported) was not crossed at this second interim analysis
[d] The stopping boundary for statistical significance (0.0164) was not crossed at this third interim analysis
[e] Stratified Cox proportional hazard model
Note: Cells shaded in blue indicate results previously considered by the PBAC.

Figure 2: Overall survival KM plot – CM816: 4-year update



Source: Figure 23, p111 of the submission
[a] Reasons for OS events (deaths) in all treated patients in the neoNIVO vs neoChemo arms (N = 176 in each arm) were disease (23% vs 33%), study drug toxicity (0% vs 2%), unknown (3% vs 3%), and other (7% vs 5%).
[b] The stopping boundary for statistical significance (0.0164) was not crossed at this third interim analysis. [c-e] 95% CI: [c] 50.4–NR; [d] 63–77; [e] 50–65
Note: The number of events were not reported in the submission or in the CM816 clinical study report

6.34 Other secondary outcomes in CM77T included pathological complete response (pCR)[5] rate and major pathological response (MPR[6]). The submission claimed that pCR has been demonstrated to correlate with survival after neoChemo and surgical resection of tumour (Mouillet 2012), and that MPR has been proposed as an alternate surrogate marker for OS (Hellmann 2014), but emphasised that no claim was being made on the basis of pCR as a surrogate for OS and instead argued that EFS was a more patient relevant outcome. While the PBAC has previously considered the outcome of EFS in its consideration of neoNIVO in NSCLC at the March 2023 and July 2023 PBAC meetings, it was unclear if it was considered to be the more patient relevant outcome. Instead, in the absence of mature OS data, the PBAC has previously noted that time to death or metastatic disease (TTDM) was a clinically meaningful outcome (paragraph 7.8, nivolumab PSD, March 2023 PBAC meeting).

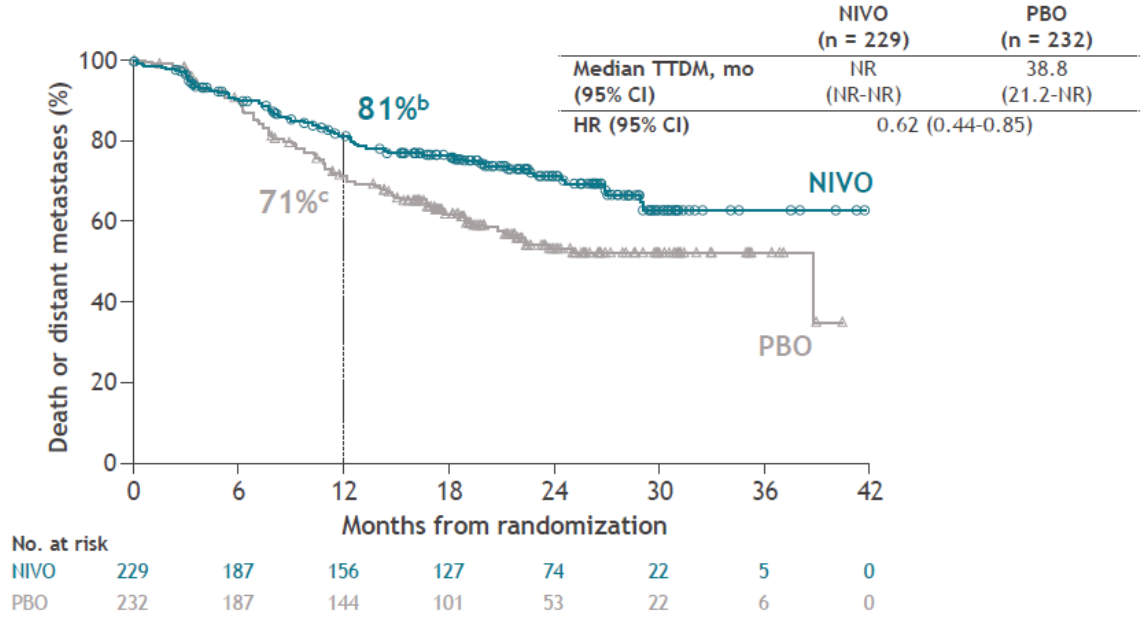
6.35 The percentage of patients with a pCR was 25.3% in the periNIVO arm and 4.7% in the neoChemo arm (odds ratio [OR] = 6.64; 95% CI: 3.40, 12.97). The percentage of patients with a MPR was 35.4% in the periNIVO arm and 12.1% in the neoChemo arm (OR = 4.01; 95% CI: 2.48, 6.49). For comparison, the magnitude of pCR benefit (OR = 13.9 ,99% CI 3.4, 55.75) and MPR benefit (OR = 5.7, 95% CI 3.2, 10.3) of neoNIVO compared to neoChemo in CM816 was numerically superior to the magnitude of pCR and MPR benefit of periNIVO compared to neoChemo in CM77T. However, as noted above, the evidence from CM816 remained insufficient for a claim of statistically significant improvement in OS. As such, if pCR and MPR were believed to be predictors of OS, given the lower pCR and MPR benefit for periNIVO in CM77T compared to neoNIVO in CM816, it may be inferred that it would be even less likely that the OS results in CM77T would be statistically significant.

6.36 Results for TTDM are presented in Figure 3.

[5] Defined as the number of randomised subjects with absence of residual viable tumour in lung and lymph nodes as evaluated by BIPR, divided by the number of randomised subjects for each arm.

[6] Defined as the number of randomised patients with ≤10% residual viable tumour in lung and lymph nodes as evaluated by BIPR, divided by the number of randomised patients for each treatment group. Subjects without an evaluable sample (e.g., cancelled surgery, withdrew consent) were counted as non-responders.

Figure 3: Time to death or distant metastases Kaplan-Meier curve – CM77T



Source: Figure 13, p 93 of the submission
Abbreviations: HR = hazard ratio; TTDM = time to death or distant metastases; NIVO = perioperative nivolumab; PBO = placebo (neoadjuvant chemotherapy arm).
[a] Time between the date of randomisation and the first date of distant metastasis or the date of death in the absence of distant metastasis per investigator assessment.
[b-c] 95% CI: [b] 75–86; [c] 65–77
Note: TTDM was an exploratory endpoint of CM77T and thus results should be interpreted with caution.

6.37 In CM77T, patients randomised to periNIVO reported a lower risk of distant metastases or death compared to patients randomised to the neoChemo arm (HR=0.62; 95% CI 0.44, 0.85). TTDM was an exploratory endpoint of CM77T and thus results should be interpreted with caution. The submission noted that TTDM data was consistent with the assessment of EFS and supported a conclusion that periNIVO delays the development of distant metastases or death compared with neoChemo.

6.38 Health-related quality of life (HRQoL) was assessed using the 3-level version of the EuroQol 5 dimension (EQ-5D-3L) questionnaire. Patients in both treatment arms had a slight worsening in EQ-5D-3L scores reported during the neoadjuvant treatment period followed by a worsening at the post-surgical visit with subsequent improvements during the adjuvant treatment period. EQ-5D-3L visual analogue scores (VAS) appeared to slightly favour neoChemo over periNIVO in the neoadjuvant treatment period and post-surgical visit, however overall no significant difference in HRQoL was observed between treatment arms.

6.39 Results for the exploratory subgroup analyses of EFS in CM77T are summarised in Table 12.

Table 12: Event-free survival: results of subgroup analysis in CM77T with whole trial population results and complement results

	PeriNIVO		Neo chemo			Test for p-value
	n/N (%)	Median time-to-event (95% CI)	n/N (%)	Median time-to-event (95% CI)	Hazard ratio (95% CI)	
Interim analysis 1: median follow-up 25.4 months						
Randomised/ITT	76/229 (33.2)	NA (28.94, NA)	113/232 (48.7)	18.43 (13.63, 28.06)	**0.58 (0.43, 0.78)**	NA
Stratification parameter: disease stage at study entry						
Stage II	22/81	NA (22.60, NA)	27/81	NA (24.18, NA)	0.81 (0.46, 1.43)	0.1725
Stage III	54/148	30.23 (26.91, NA)	86/151	13.40 (9.79, 17.74)	0.51 (0.36, 0.72)	
Stratification parameter: PD-L1 expression						
<1%	34/93	29.04 (21.39, NA)	44/93	19.81 (13.86, NA)	0.73 (0.47, 1.15)	0.2683
≥1%	39/128	NA (28.94, NA)	63/128	15.80 (9.33, 35.06)	0.52 (0.35, 0.78)	
1-49%	30/80	30.23 (20.01, NA)	33/76	NA	0.76 (0.46, 1.25)	NA
≥50%	9/45	28.06 (11.01, NA)	30/52	7.98 (6.28, 23.72)	0.26 (0.12, 0.55)	
Stratification parameter: tumour histology						
Squamous	31/116	NA	56/118	16.99 (10.15, NA)	0.46 (0.30, 0.72)	0.1344
Non-squamous	45/113	28.94 (21.39, NA)	57/114	18.43 (13.60, 28.06)	0.72 (0.49, 1.07)	
Subgroup: ECOG PS						
0	46/147	NA (27.01, NA)	68/141	20.07 (12.58, NA)	0.57 (0.39, 0.83)	0.8223
1	30/82	29.04 (22.60, NA)	45/91	17.28 (10.55, 35.06)	0.61 (0.39, 0.97)	
Subgroup: Sex						
Male	53/167	NA (28.94, NA)	78/160	16.72 (10.15, NA)	0.53 (0.37, 0.75)	0.3726
Female	23/62	30.23 (19.68, NA)	35/72	18.76 (14.72, 35.06)	0.71 (0.41, 1.20)	

Source: Table 52, p91 of the submission, Figure 14.2.1.6.1 CM77T CSR and compiled/calculated during the evaluation
Abbreviations: BICR = blinded independent central review; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; EFS = event-free survival; ITT = intention to treat; NA = not available/not reached; Neo chemo = neoadjuvant chemotherapy; PeriNIVO = perioperative nivolumab
Note: Bolded values indicate statistically significant results.

6.40 In the PD-L1 expression negative subgroup (<1%), the 95% confidence interval (CI) around the EFS HR included the null and it was unlikely that there was any statistically significant benefit associated with periNIVO over neoChemo. The EFS benefit was more marked in patients who expressed PD-L1 (PD-L1 ≥1% or ≥50%). Acknowledging the small sample size of some of the subgroups and exploratory nature of the analyses, the data suggested the relative reduction in hazard of an EFS event associated with periNIVO over neoChemo was larger for tumours which express PD-L1, especially those with high levels of PD-L1 expression (≥50%).

6.41 The PBAC has previously considered PD-L1 status in the March and July 2023 neoNIVO submissions. The PBAC noted that PD-L1 subgroup analyses indicated the relative reduction in hazard of an EFS event for neoNIVO appeared larger for tumours that express PD-L1 but considered that restricting access based on PD-L1 status would not be appropriate (paragraph 7.7, nivolumab PSD, March 2023 PBAC meeting).

6.42 The magnitude of relative EFS benefit associated with periNIVO over neoChemo was more pronounced in patients with Stage IIIA disease (N=148, HR 0.51; 95% CI: 0.36, 0.72) compared to those with earlier Stage II disease (N=81, HR 0.81; 95% CI: 0.46, 1.48). Interpretation of these results requires caution given the small sample size of the Stage IB/II disease subgroup.

6.43 The PBAC has previously considered disease stage for the March 2023 neoNIVO submission. The PBAC noted that the magnitude of relative EFS benefit associated with neoNIVO over neoChemo appeared more pronounced in patients with Stage IIIA disease compared to those with earlier Stage IB/II disease but considered that due to a small sample size these results remain inconclusive (paragraph 7.7, nivolumab PSD, March 2023 PBAC meeting).

Indirect treatment comparisons

6.44 For the main comparator proposed in the PSCR, neoNIVO, the evidence was based on an anchored ITC between the CM77T and CM816 trials. The results of the ITC are summarised in Table 13. The primary ITC analysis used CM816 data from the first interim analysis (median follow-up 29.5 months) for the most consistent duration of follow-up between trials. A secondary analysis using the most recent CM816 data (median follow-up 57.6 months) was also presented.

6.45 There were several observed differences in patient, disease and study characteristics that may introduce risk of bias for the indirect comparison between CM77T and CM816, which included:

- The proportion of male patients differed substantially between CM77T (71%) and CM816 (49%), and the CM77T trial enrolled approximately half as many Asian patients (25%) than in CM816 (50%);
- Most patients (86%, 396/458) enrolled in CM77T received four cycles of neoadjuvant treatment, compared with CM816 where a maximum of three neoadjuvant cycles were permitted. In addition, of the patients enrolled in the periNIVO arm of CM77T, only 62% went on to receive adjuvant nivolumab. It is uncertain to what extent (if any) the additional cycle of neoadjuvant treatment in the common comparator arm confounded the comparative treatment efficacy between periNIVO and neoNIVO;
- Different staging criteria were used (CM816; AJCC 7th edition, CM77T; AJCC 8th edition), making a direct comparison of staging at baseline problematic. Notably, some patients that were categorised as Stage IIIA (T3N2 and T4N2) in CM816 would now be categorised as Stage IIIB under AJCC 8th edition. There were 43 patients (19%, 43/229) in the periNIVO arm of CM77T that had Stage IIIB disease, which were excluded as per protocol in CM816. Acknowledging the different staging criteria, patients in CM77T generally had more severe disease. Given that there was some evidence in the subgroup analysis of CM77T that the magnitude of relative EFS benefit was more pronounced for patients with more progressed disease compared to earlier Stage II disease (see Table 12), this difference may favour periNIVO in the indirect comparison, though the magnitude of effect is uncertain; and
- *EGFR* testing was required for all non-squamous patients in CM77T, compared with CM816 where *EGFR* testing was not part of the screening requirement.

Therefore, it is possible that some patients with *EGFR* mutation may have been included in CM816. The impact of this difference was unclear.

Table 13: Indirect treatment comparisons of EFS for periNIVO versus neoNIVO – CM77T and CM816

	PeriNIVO		NeoChemo		NeoNIVO		EFS hazard ratio (95 % CI)
Trial	n/N with event (%)	Median time-to-event (95% CI)	Common reference n/N with event	Median time-to-event (95% CI)	n/N with event (%)	Median time-to-event (95% CI)	
Primary assessment: CM77T & CM816 Interim analysis 1							
CM77T	76/229 (33)	NR (28.9, NA)	113/232 (49%)	18.4 (13.6, 28.1)	-	-	0.58 (0.43, 0.78)
CM816	-	-	87/179 (49%)	20.8 (14.0, 36.7)	64/179 (36)	31.6 (30.2, NA)	0.63 (0.45, 0.87)
Indirect estimate of effect of periNIVO vs neoNIVO using neoChemo as the common reference							0.92 (0.59, 1.44)
Secondary assessment: CM77T Interim analysis 1; CM816 4-year update							
CM77T	76/229 (33)	NR (28.9, NA)	113/232 (49%)	18.4 (13.6, 28.1)	-	-	0.58 (0.43, 0.78)
CM816	-	-	NA/179	18.4 (14.0, 26.7)	NA/179	43.8 (31.6, NA)	0.66 (0.49, 0.90)
Indirect estimate of effect of periNIVO vs neoNIVO using neoChemo as the common reference							0.88 (0.57, 1.35)

Source: Table 70, p116 of the submission
Abbreviations: CI = confidence interval; EFS = event-free survival; NA = not assessable; neoChemo = neoadjuvant chemotherapy; NR = not reached; periNIVO = perioperative nivolumab

6.46 The EFS hazard ratio reported for the primary ITC of periNIVO versus neoNIVO was 0.92 (95% CI: 0.59, 1.44) which was not lower than the nominated MCID threshold of ≤0.85. However, noninferiority should not be assessed based on the point estimate, and no noninferiority margin was proposed to allow a formal test for noninferiority. The reported EFS hazard ratio also had a wide confidence interval, indicating a high level of uncertainty around the estimated effect size. There was also a small difference in the median EFS in the common comparator (18.4 months in CM77T and 20.8 months in CM816). It was unclear if this difference was significant, but may potentially bias the results against neoNIVO.

6.47 Similar to the primary analysis, the reported secondary analysis EFS hazard ratio was associated with a high level of uncertainty. The median EFS in the common comparator was more comparable in the secondary ITC compared to the primary ITC. However, noting that the EFS HR point estimate was less favourable for neoNIVO at the 4-year update than in the interim analysis, it was possible that the results may be biased in favour of periNIVO in the secondary ITC and it was plausible that at a similar follow-up, CM77T may also report a less favourable EFS HR than at the interim analysis.

6.48 A comparison of surgical outcomes from CM77T and CM816 is presented in Table 14.

Table 14: Summary of surgical outcomes: CM77T and CM816

	CM77T		CM816	
	periNIVO (N=229)[a]	neoChemo (N=232)	neoNIVO (N=179)	neoChemo (N=179)
Patients with definitive surgery, n (%)	178 (78%)	178 (77%)	149 (83%)	135 (75%)
Patients with cancelled definitive surgery, n (%)	46 (20%)	50 (22%)	28 (16%)	37 (21%)
Disease progression	13 (6%)	22 (10%)	12 (7%)	17 (10%)
Patient refusal	11 (5%)	8 (3%)	-	-
Surgeon decision	8 (4%)	6 (3%)	-	-
Adverse event	7 (3%)	4 (2%)	2 (1%)	1 (0.6%)
Other	7 (3%)	10 (4%)	14 (8%) [b]	19 (11%) [b]
Disease progression	13 (6%)	22 (10%)	12 (7%)	17 (10%)
Patients with delayed surgery, n (%)	36 (16%)	33 (14%)	31 (21%)	24 (18%)
Adverse event	8 (4%)	7 (3%)	6 (4%)	9 (7%)
Duration of surgery, minutes: Median (IQR)	216.5 (164.0–300.0)	223.0 (150.0–299.0)	185.0 (133.0–260.0)	213.5 (150.0–283.0)
Length of delay in surgery, weeks: Median (IQR)	1.7 (0.6–3.0)	1.1 (0.4–2.9)	2.0 (0.6–3.0)	2.4 (1.0–3.7)
Type of surgery, n (%)				
Lobectomy	142 (80%)	128 (72%)	115 (77%)	82 (61%)
Bilobectomy	14 (8%)	23 (13%)	3 (2%)	4 (3%)
Pneumonectomy	16 (9%)	24 (14%)	25 (17%)	34 (25%)
Completeness of resection, n (%)				
R0 (no residual tumour)	159 (89%)	161 (90%)	124 (83%)	105 (78%)
R1 (microscopic residual tumour)	17 (10%)	11 (6%)	16 (11%)	21 (16%)
R2 (macroscopic residual tumour)	2 (1%)	6 (3%)	5 (3%)	4 (3%)
Median length of hospital stay — days (IQR)	9.0 (6.0–13.0)	9.0 (6.0–12.0)	10.0 (7.0–14.0)	10.0 (7.0–15.0)

Source: Table 78, p125 of the submission and pp36-37 of Supplement to Forde et al., 2022

Abbreviations: neoChemo = neoadjuvant chemotherapy; neoNIVO = neoadjuvant nivolumab; periNIVO = perioperative nivolumab

[a]: Surgery status not reported for 2 patients (0.9%)

[b] Includes patient refusal, unresectability, and poor lung function

6.49 The proportion of patients receiving a nivolumab regimen that received definitive surgery was higher in CM816 (83%) compared with CM77T (77%). The submission noted that in CM77T where four cycles of neoadjuvant treatment were given, a higher percentage of patients achieved more complete resection of tumour (R0, no residual tumour) compared with CM861 where three cycles of neoadjuvant treatment were given. However, it was unclear if the differences were statistically significant or clinically meaningful.

6.50 Overall, the evaluation considered that it was difficult to draw a reliable conclusion based on the ITC between CM77T and CM816 as there were several transitivity issues, the point estimates did not meet the proposed MCID for EFS, and a noninferiority margin was not available to allow a for formal assessment of noninferiority. Nonetheless, the evaluation considered results from the ITC of periNIVO versus neoNIVO indicated periNIVO was likely no different to neoNIVO in terms of EFS.

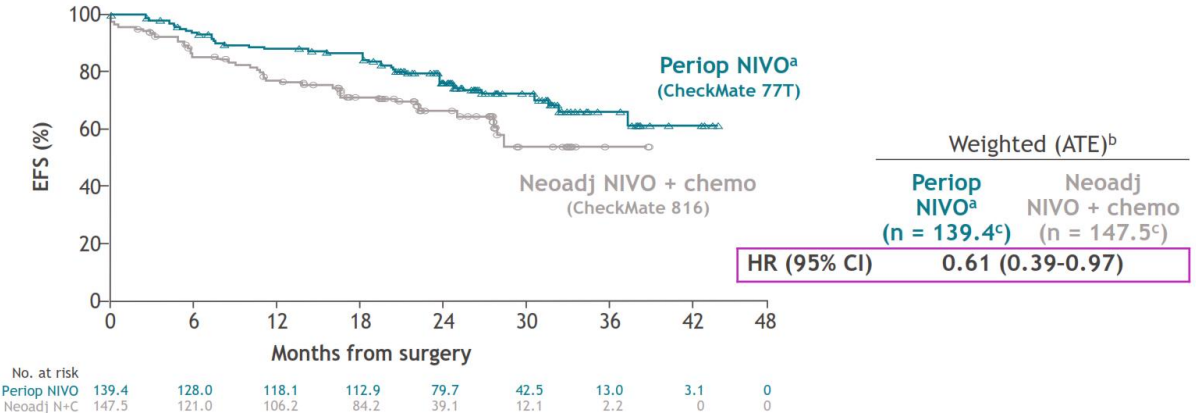
6.51 The PSCR acknowledged that there was transitivity issues associated with the ITC between CM77T and CM816 presented in the submission. However, the PSCR considered strategies implemented by the submission mitigated their impact and

overall considered the transitivity issues did not inherently preclude the validity of conducting the ITC. The Sponsor also noted that a Propensity Score Matching Indirect Comparison (PSM ITC) of periNIVO versus neoNIVO using patient-level data from CM77T and CM816 was recently presented at the World Conference on Lung Cancer (WCLC) (Forde 2024[7]). The PSCR noted that the propensity score weighting analyses (average treatment effect for the treated [ATT] and average treatment effect [ATE]) were performed and adjusted for baseline demographics and disease characterises between study populations and reduced the confounding effects of these factors. Adjustments were made for: sex, race, clinical stage, tumour histology, PD-L1 expression, age, Eastern Cooperative Oncology Group performance status (ECOG PS) and smoking status. Results for these analyses are shown in Figure 4 and

[7] Forde, P., Peters, S., Doninton, J., Meadows-Shroshire, S., Tran, P., Lucherini, S., Erdmannm C., Sun, H., Cascone, T. 2024. Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816. World Conference on Lung Cancer. September 7-10; San Diego, SA, USA. Presentation number 3589.

6.52 Table 15. For both analyses, approximately 40% reduction in risk of disease recurrence or death after surgery was observed in patients who received ≥ 1 dose of adjuvant NIVO following neoNIVO + chemo treatment and surgery compared with those who did not receive adjuvant NIVO. The ESC considered the results from Forde 2024 were unlikely to be a reliable basis to support a claim of superiority in terms of EFS, as proposed in the PSCR (paragraph 6.55).

Figure 4: Event-free survival from definitive surgery (BICR)



Source: PSCR (p4); Forde et al 2024

Abbreviations: ATE = average treatment effect; BICR = blinded independent central review; CI = confidence interval; EFS = event-free survival; HR = hazard ratio

[a]Includes only patients who received ≥ 1 dose of adjuvant NIVO.

[b]ATE: varying weights were applied to all patients in both neoadjuvant.

NIVO + chemo arm (CheckMate 816) and perioperative NIVO (CheckMate 77T) to make them comparable to one another.

[c]N values fractional due to weighting. dATT: varying weights were applied to patients in the neoadjuvant NIVO + chemo arm (CheckMate 816) to make them comparable to those in the perioperative NIVO arm (CheckMate 77T).

Notes: In the unweighted analysis population, 89 patients (64%) completed adjuvant therapy, and median number of doses (range) was 13.0 (1–13). Unweighted landmark EFS from surgery among all patients who had surgery (regardless of whether they received adjuvant NIVO in CheckMate 77T) for periop NIVO vs neoadj NIVO + chemo: HR = 0.82 (95% CI, 0.55–1.21).

Table 15: Summary of indirect treatment comparisons for periNIVO versus neoNIVO

ITC method	EFS HR (95% CI)
Bucher using neoChemo as common comparator (presented in submission)	0.92 (0.59, 1.44)
Propensity score matched CM77T and CM816: ATE	0.61 (0.39, 0.97)
Propensity score matched CM77T and CM816: ATT	0.59 (0.38, 0.92)

Source: PSCR (p4); Forde et al 2024

Abbreviations: ATE = average treatment effect; ATT = average treatment effect for the treated; BICR = blinded independent central review; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; ITC = indirect treatment comparison

Clinical claim

6.53 The submission claimed that periNIVO offers 'at least noninferior, and potentially superior efficacy' and noninferior safety compared with neoNIVO.

6.54 The ESC considered that the clinical claim of 'at least noninferior, and potentially superior' efficacy of periNIVO compared to neoNIVO was uncertain and likely not supported. The ESC noted the results from the ITC of periNIVO versus neoNIVO presented in the submission (HR=0.92; 95% CI: 0.59, 1.44) was associated with wide confidence intervals, indicating a high level of uncertainty around the estimated effect size. The ESC agreed with the evaluation that it was difficult to draw a reliable conclusion based on the ITC between CM77T and CM816 as there were several transitivity issues (e.g. differences in proportion of males, number of doses of chemotherapy in the common comparator, and different NSCLC staging criteria), the point estimates did not meet the proposed MCID for EFS, and no nominated noninferiority margin was nominated to allow an assessment of noninferiority.

6.55 The ESC noted the PSCR referenced a PSM ITC of periNIVO versus neoNIVO using patient-level data from CM77T and CM816 (Forde et al 2024[8]) which adjusted for baseline demographics and disease characteristics between study populations. The ESC noted the EFS HRs for the ATE and ATT analyses were 0.61 (95% CI: 0.39−0.97) and 0.59 (95% CI 0.38−0.92) respectively, which were more optimistic that the HR presented in the submission using the Bucher approach (HR 0.92, 95% CI: 0.59−1.44; paragraph 6.51). However, the ESC noted that the PSM ITC had not undergone formal evaluation or independent review, which raised uncertainty of the reliability of the results. Further, sufficient detail was not provided (i.e. the patient dataset and propensity score weights) to verify or replicate the results presented in Forde 2024. It was noted that the sample size in the periNIVO arm was reduced from 228 patients to 139, and in the neoNIVO arm from 176 patients to 147. The information for these excluded patients was not provided, and therefore it is unclear what impact the excluded patients had on the estimated HR. The ESC also noted that in this ITC the CM77T group appeared to be limited to those who were deemed suitable for adjuvant nivolumab, while the CM816 group consisted of all participants. Given that only 62% of patients in CM77T received adjuvant nivolumab, it is conceivable that this would

[8] Forde, P., Peters, S., Doninton, J., Meadows-Shroshire, S., Tran, P., Lucherini, S., Erdmannm C., Sun, H., Cascone, T. 2024. Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816. World Conference on Lung Cancer. September 7-10; San Diego, SA, USA. Presentation number 3589.

bias the results in favour of CM77T, as patients in that trial who did not respond to or tolerate neoadjuvant nivolumab were excluded from the comparison. Overall, the ESC considered the results from Forde 2024 were unlikely to be a reliable basis to support a claim of superiority in terms of EFS as proposed in the PSCR. The Pre-PBAC Response provided further detail on the patients included in the PSM ITC analyses; however, the PBAC considered the concerns regarding the analyses raised by the ESC remained.

6.56 The ESC considered that the claim of noninferior safety between periNIVO and neoNIVO was not reasonable given that a higher proportion of patients treated with periNIVO in CM77T experienced any AEs (all-causality) compared with patients treated with neoNIVO in CM816 (50% versus 43%, respectively). In addition, the proportion of patients that experienced any AEs resulting in treatment discontinuation (all-causality) in the periNIVO arm in CM77T was more than double that of the neoNIVO arm in CM816 (25% versus 10%; RR=2.3 [95% CI 1.1, 2.9: p<0.001]). However, given the longer duration of exposure to periNIVO compared to neoNIVO, it is not surprising that periNIVO would have a higher proportion of patients experiencing AEs resulting in treatment discontinuation. The Pre-PBAC Response stated that given the proportion of AEs, including AEs resulting in treatment discontinuation, were higher in patients treated with periNIVO compared to neoNIVO, a claim of inferior (but manageable) safety for neoNIVO compared to neoNIVO was appropriate.

6.57 The ESC noted that, given the uncertainty regarding the clinical claim of 'at least noninferior and possibly superior' efficacy, the use of additional doses of nivolumab in the periNIVO regimen provided an unclear clinical benefit with an increase in toxicity.

6.58 The PBAC considered the claim that periNIVO offers at least non-inferior and potentially superior comparative effectiveness compared with neoNIVO was not adequately supported by the data.

6.59 The PBAC considered the claim that periNIVO has inferior safety compared with neoNIVO was supported by the data.

Economic analysis

6.60 The PSCR acknowledged that due to its recent PBS listing, neoNIVO was the most appropriate main comparator, for which a clinical claim of at least noninferiority, and potentially superior efficacy, for periNIVO versus neoNIVO was made by the submission. The PSCR presented a cost-minimisation for the comparison of periNIVO versus neoNIVO, which the PSCR stated was a conservative approach given that Forde et al 2024 reported superiority for periNIVO compared to neoNIVO. Given a cost-minimisation approach (CMA) was adopted, issues related to the cost-utility analysis were not addressed in the PSCR.

Cost minimisation: periNIVO versus neoNIVO

6.61 The CMA presented in the PSCR was based on equivalent total costs for neoNIVO and periNIVO over the total duration of therapy for each treatment regimen. The total cost of therapy included drug costs for nivolumab and chemotherapy, and administration costs.

6.62 The proposed equi-effective doses are:

- PeriNIVO: 360 mg neoadjuvant nivolumab every 3 weeks for 3.65 cycles in combination with platinum-based chemotherapy followed by 480 mg adjuvant nivolumab every 4 weeks for 10.12 cycles; and
- NeoNIVO: 360 mg neoadjuvant nivolumab every 3 weeks for 2.91 cycles in combination with platinum-based chemotherapy.

6.63 In the CM77T and CM816 trials, patients could be treated with different combinations of platinum-based chemotherapy. For the purposes of the CMA, the chemotherapy regimens accounted for were those most frequently administered in the CM77T and CM816 trials. These were carboplatin and paclitaxel in the CM77T trial and cisplatin and pemetrexed in the CM816 trial.

6.64 Administration costs for each infusion was assumed to be $123.05 (MBS item 13950). Infusions of nivolumab and chemotherapy conducted at the same visit were assumed to accrue the administration cost of a single infusion. The duration of treatment for periNIVO and neoNIVO were based on the mean doses reported in each of the pivotal trials (CM77T and CM816) for the nivolumab plus chemotherapy treatment arms.

6.65 The calculated AEMP for periNIVO in the PSCR was dependent on the proportion of periNIVO patients expected to continue on to adjuvant treatment (assumed to be 62.28%, based on CM77T). The ESC noted that should the proportion of patients commencing adjuvant treatment be higher in Australian clinical practice, the calculated cost minimised AEMP would decrease, and vice versa.

6.66 The ESC noted that the increased rate of AEs in patients treated with periNIVO in comparison with neoNIVO was not considered in the CMA, with the PSCR maintaining the claim that periNIVO has non-inferior safety compared with neoNIVO. The ESC considered this was likely to be an unreasonable approach.

6.67 The ESC also considered it was unclear whether it was reasonable for different chemotherapy regimens to be used in the neoNIVO (cisplatin and pemetrexed) and periNIVO (carboplatin and paclitaxel) cost per course calculations, as these are unlikely to differ in clinical practice given the shared patient population. The inclusion of chemotherapy was also inconsistent with the submission's financial estimates, in which chemotherapy costs were not included. However, the inclusion of these costs did not significantly impact the calculated AEMP, with equal chemotherapy costs changing the AEMP for periNIVO by <1%.

6.68 The two-weekly (Q2W) dosing option for adjuvant NIVO was not considered in the CMA, which was inconsistent with the financial estimates presented in the submission in which 12% of adjuvant continuing periNIVO patients were assumed to receive Q2W dosing. Inclusion of the additional administration costs for Q2W dosing would result in a lower cost minimised AEMP.

6.69 Overall, the ESC considered the assumed equi-effective dosing and costs for the CMA appeared largely reasonable, however it would be appropriate to include increased AE costs and Q2W dosing for periNIVO in the cost-minimised AEMP. It should be noted that the presented CMA was unable to be evaluated in full, and the overall appropriateness of a CMA approach is dependent upon the acceptance of non-inferiority.

6.70 The Pre-PBAC Response provided a revised CMA. The revised CMA incorporated the cost of Grade 3/4 AEs that were reported in ≥2% of patients in either the periNIVO arm of CM77T or the neoNIVO arm of CM816.

6.71 The CMA was also revised to include Q2W (12%) and Q4W (88%) dosing.

6.72 The results of the CMA that were presented in the Pre-PBAC Response are shown in Table 16. The total cost per patient for neoNIVO was estimated to be $. The Response proposed that this resulted in an AEMP of $ per 100 mg vial for nivolumab, increased from the AEMP of $ per 100 mg vial proposed in the PSCR.

Table 16: Results of the cost-minimisation approach as presented in the Pre-PBAC Response

Component	NeoNIVO (CM816)	periNIVO (CM77T)		
		Neoadjuvant only	Neoadjuvant plus adjuvant	
			Neoadjuvant	Adjuvant
Dosing				
Proportion of patients	-	37.72%	62.28%	
Mean number of doses for Nivolumab	2.91	3.65	3.65	11.34 (weighted)[a]
Nivolumab dose (mg)	360	360	360	451 (weighted)[b]
Mean number of doses for chemotherapy	Cisplatin: 2.77 Pemetrexed: 2.93	Carboplatin: 3.60 Paclitaxel: 3.60		
Chemotherapy dose	Cisplatin: 136 mg (75 mg/m^2) Pemetrexed: 905 mg (500 mg/m^2)	Carboplatin: 724 mg (400 mg/m^2) Paclitaxel: 317 mg (175 mg/m^2 or 200 mg/m^2)		
Drug costs				
Nivolumab component				
Effective AEMP, 100 mg vial	$	$		
Nivolumab cost per patient	$	$	$	
Chemotherapy component				
AEMP	Cisplatin: $10.41 per 50 mg vial Pemetrexed: $26.54 per 500 mg vial	Carboplatin: $26.58 per 450 mg vial Paclitaxel: $36.78 per 300 mg vial		
Chemotherapy cost per patient	$218.99	$293.75		
Total drug cost per patient	$	$	$	
Administration costs				
Cost per IV infusion (MBS Item 13950, 100% fee)	$123.05	$123.05	$123.05	
Administration cost per patient	$357.96	$449.30	$1,844.09	
Adverse Event costs				
AE cost per patient	$1,044.32	$928.28	$928.28	
Cost/patient/course	**$**	**$**	**$**	

Source: Pre-PBAC Response (pp2−3) and accompanying workbook: 'Opdivo perioperative NSCLC cost-minimisation analysis_pre-PBAC.xlsx'

[a] 10.12 doses (88% of patients) assumed for Q4W dosing and 20.24 doses (12% of patients) assumed for Q2W dosing

[b] 480 mg (88% of patients) assumed for Q4W dosing and 240 mg (12% of patients) assumed for Q2W dosing

Abbreviations: AEMP = approved ex-manufacturer price; IV = intravenous; MBS, Medicare Benefits Scheme; PSCR = pre-sub-committee response

6.73 The PBAC noted the CMA provided in the pre-PBAC response had not been evaluated but considered it likely there was an error in the methodology as the approach only accounted for neoadjuvant use in a proportion of patients (37.72%) however it would be received by all patients.

Cost-utility analysis: periNIVO versus neoChemo

6.74 The submission presented a stepped economic evaluation based on the randomised trials CM77T and CM816. The type of economic evaluation presented was a cost-utility analysis (CUA), that compared periNIVO versus neoChemo for the treatment of patients with resectable (tumours ≥4 cm or node positive) NSCLC. Given the change in main comparator to neoNIVO and the presentation of a CMA based on the claim of noninferiority in the PSCR, the results of the CUA are not presented.

Drug cost/patient/course

6.75 Based on the revised financials included in the pre-PBAC response (which incorporated the effective price proposed in paragraph 6.72), the average nivolumab cost per patient in Year 1 was $[redacted] for periNIVO and $[redacted] for neoNIVO[9]. The PBAC noted the average cost per patient for periNIVO was higher than for neoNIVO, likely due to the incorrect methodology applied in the CMA (see paragraph 6.73).

Estimated PBS usage & financial implications

6.76 This submission was not considered by DUSC.

6.77 At the time of ESC consideration, revised financial estimates with the updated price and substitution for neoNIVO proposed in the PSCR were not available. Therefore, the ESC was unable to provide guidance on the reliability of the methods used to derive the utilisation and financial estimates and the structure of the estimates model, as the final model was not available at the time of consideration.

6.78 The financial analysis provided in the submission took an epidemiological approach to estimate the financial impacts of the proposed listing of periNIVO for the neoadjuvant treatment of patients with resectable NSCLC.

6.79 The financial estimates shown only consider the use of the immunotherapy component of treatment and not any chemotherapy agents used in combination with or prior to immunotherapy, or as neoadjuvant or adjuvant treatment of resectable NSCLC. This approach was consistent with the July 2023 and March 2024 neoNIVO submissions.

6.80 The key inputs in the financial analysis provided in the submission are summarised in Table 17.

[9] Calculated as $[redacted]/1,277 and $[redacted]/1,277 (see Table 18)

Table 17: Key inputs for financial estimates

Data	Value and Source	Comment
Eligible population		
Incident cases of lung cancer	Source: Age-standardised rate of 56.20 per 100,000 (AIHW 2023) applied to ABS population.	The evaluation considered that this was reasonable.
% meeting other PBS criteria	86.6% of lung cancer is NSCLC (AIHW 2022)	The evaluation considered that this was reasonable. These values were consistent with the neoNIVO March 2023 submission (Table 25, nivolumab PSD, March 2023 PBAC Meeting).
	22.4% (squamous); 77.6% (non-squamous) Source: PIvOTAL study (Castro et al., 2017)	
	83.50% Proportion of non-squamous NSCLC patients with no known EGFR/ALK (PIvOTAL study)	
	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% -Stage IIIB: 40.82% Source: AIHW CDiA 2023, Provencio et al., 2019	There is some uncertainty associated due to updates in staging criteria (AJCC 7th to AJCC 8th)
	80% of patients with resectable tumours Source: Assumption	Consistent with previous neoNIVO March 2023 submission (Table 25, nivolumab PSD, March 2023 PBAC Meeting).
	82.82% ECOG PS 0-1 Source: Weighted distribution calculated by PS on WHO scale Kawaguchi 2010; Stage distribution from AIHW, CDiA 2022, Provencio et al., 2019,	Uncertain. The PBAC has previously considered for patients with Stage IIA-IIIA NSCLC, an estimate of 80% of patients with a WHO PS of 1 or less would be appropriate in the adjuvant setting (Table 20, atezolizumab PSD, July 2022 PBAC Meeting).
Treatment utilisation		
Uptake rate of (neoadjuvant) periNIVO	[redacted]% (Year 1−6, and across Stage II-IIIB, excluding surgery alone and neoNIVO as treatment options) Source: Sponsor run March 2024 advisory board of 6 oncologists.	The PBAC previously advised the uptake rate may be lower than estimated (72.5% for eligible Stage IB, II and IIIA patients) and advised that an uptake of 30−40% per annum in the first 2 years of listing may be a more reasonable estimate of uptake (para. 5.10, nivolumab PSD July 2023 PBAC Meeting). This parameter was revised to [redacted]% in the Pre-PBAC Response.
Proportion of patients that go on to receive adjuvant NIVO	62.28%; Source: CM77T CSR	The evaluation considered that this was reasonable.
Adjuvant NIVO Q4W vs Q2W utilisation	Q4W: 88%; Q2W: 12% Source: 2019 NIVO minor submission for dosing regimens	The estimated split is uncertain, however the PBAC previously considered that it was reasonable to assume that the majority of patients would be prescribed the 480mg Q4W dosing if available (para. 5.4, nivolumab PSD, March 2019 PBAC meeting).

Source: Table 146, Table 152, Table 155, pp237-238, pp242-243, pp245-246 of the submission, Excel workbook 'Nivolumab Perioperative NSCLC Utilisation and Cost Model'.

Abbreviations: AIHW = Australian Institute of Health and Welfare; CDiA = Cancer Data in Australia; CSR = clinical study report; DUSC = Drug Utilisation Sub-committee; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PS = performance status; PSD = public summary document; NIVO = nivolumab; WHO = World Health Organization.

6.81 The ESC noted that the estimated patient numbers for periNIVO in the submission were higher than the number of patients estimated for neoNIVO in the March 2024 neoNIVO submission. This was largely due to:

- The inclusion of Stage IIIB patients, which were not included in the July 2023 neoNIVO financial estimates;
- The uptake rate for periNIVO ([redacted]%) was higher than the uptake rate for neoNIVO (72.5%), which was not reasonable; and
- The epidemiological approach used to estimate atezolizumab and durvalumab patients, which was also not reasonable and added to the total patient pool.

6.82 Revised financial estimates were provided in the Pre-PBAC Response. Changes made include:

- A reduced periNIVO price, from $[redacted] to $[redacted] AEMP per 100 mg vial;
- The inclusion of cost-offsets associated with the substitution of neoNIVO (all patients treated with periNIVO are assumed to be offset by neoNIVO); and
- A reduced uptake rate (Years 1 – 6) from [redacted]% to [redacted]%.
- Removal of cost-offsets associated with metastatic pembrolizumab, adjuvant atezolizumab and durvalumab (as this would have been accounted for in the neoNIVO listing).

6.83 The predicted use and financial implications associated with the proposed listing is summarised in Table 18.

Table 18: Estimated use and financial implications for periNIVO, and the July 2023 neoNIVO resubmission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Pre-PBAC Response						
Estimated extent of use of periNIVO						
Total treated patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total number of scripts	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of periNIVO						
Total cost to the PBS/RPBS, less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications for other medicines (reduced used of neoNIVO)						
Reduction in cost to the PBS/RPBS, less copayments	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net financial implications of periNIVO						
Net cost to PBS/RPBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Net cost to MBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net cost to PBS/RPBS/MBS	$[redacted][5]	$[redacted][5]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net financial implications of periNIVO (submission)						
Net cost to PBS/RPBS[a]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Net cost to MBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net cost to PBS/RPBS/MBS	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Estimated extent of use of neoNIVO, July 2023 re submission						
Total number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of neoNIVO, July 2023 re submission						
Total cost to the PBS/RPBS less copayments	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]

Source: Pre-PBAC Response and accompanying excel workbook 'Nivolumab Perioperative NSCLC U&C model_Pre-PBAC.xls', Table 162, p252 of the submission. Table 9, nivolumab PSD, March 2024 PBAC meeting.

Abbreviations: MBS = Medicare Benefits Scheme; neoNIVO = neoadjuvant nivolumab; PBS = Pharmaceutical Benefits Scheme; periNIVO = perioperative nivolumab; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] Based on published price of durvalumab and atezolizumab and estimated effective price of pembrolizumab

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] 10,000 to < 20,000

[3] $40 million to < $50 million

[4] $20 million to < $30 million

[5] $10 million to < $20 million

[6] $0 to < $10 million

[7] $30 million to < $40 million

6.84 The net cost to the PBS/RPBS of listing periNIVO was estimated in the Pre-PBAC Response to be $10 million to < $20 million in Year 1, increasing to $10 million to < $20 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing.

6.85 The financial estimates did not include any grandfathered patients.

6.86 It was noted that Stage IB patients, which were included in the March and July 2023 neoNIVO submissions, were not included in the current submission. Conversely, Stage IIIB patients, which were not included in March and July 2023 neoNIVO submission were included in the current submission. The proposed restriction for periNIVO is not stage specific and instead the eligibility criteria states that patient must have resectable tumours ≥4 cm or node positive NSCLC. Under the AJCC 8th edition description, patients with a tumour of >3 to ≤ 4 cm tumour can still be classified as

T2a, and patients with T2a N0 tumours would still be classified as IB. Therefore, Stage IB patients may be eligible for periNIVO. In addition, amongst several other changes made to the AJCC 7th edition, for N2 (T3 and T4), IIIA was upstaged to IIIB in the 8th edition. Therefore, a proportion of patients that were classified as Stage IIIA during the neoNIVO financial estimates would now be included in the Stage IIIB incident patients under the updated staging criteria. The degree of overlap between the Stage IIIA and Stage IIIB patient pools is uncertain. The ESC considered the inclusion of patients with Stage IIIB disease was in line with CM77T inclusion criteria and therefore reasonable.

6.87 The uptake rate for periNIVO ([redacted]%) was assumed to be higher in the submission than previously assumed for neoNIVO (72.5%). Furthermore, at the July 2023 PBAC meeting, the PBAC advised that an uptake rate of 30−40% per annum in the first two years of listing may be a more reasonable estimate of uptake (paragraph 5.10, nivolumab PSD July 2023 PBAC Meeting). The PSCR stated that the uptake rate proposed for periNIVO was based on an Advisory Board survey (which was provided with the submission). The PSCR also noted that a lower uptake rate for neoNIVO was recommended for the first two years of listing as the PBAC considered 'treatment with neoadjuvant nivolumab would require a change to current clinical practice with surgery being delayed…' (paragraph 5.10, nivolumab PSD, July 2023 PBAC meeting). The PSCR argued that given neoNIVO is now PBS listed, a change in clinical practice would likely be more established and consequently a lower uptake rate should not apply. The ESC considered the time required for a change in clinical practice to occur was uncertain, however would likely be longer than proposed in the PSCR. Overall, the ESC considered the uptake rate for periNIVO was unlikely to be different to the uptake estimated for neoNIVO. Based on an Advisory Board Survey, the Pre-PBAC response revised the uptake rate for periNIVO to [redacted]% (Years 1 through 6). The Response stated that while this differs to the uptake of neoNIVO, it considered the Advisory Board survey specific to periNIVO provided a reasonable estimate for the expected uptake. The Pre-PBAC Response maintained that given that neoNIVO was now PBS listed, a change in clinical practice would be more established and consequently a lower uptake rate should not apply.

Quality Use of Medicines

6.88 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), 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 irARs 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

6.89 The Sponsor indicated that it was willing to enter a risk-sharing agreement (RSA) related to expenditure in this disease state, including the potential for subsidisation caps. The PBAC has previously noted that if nivolumab were listed, it would be included in the current RSA for immunotherapy of NSCLC, with a minimal increase in the cap (paragraph 4.27, nivolumab PSD, July 2023 PBAC meeting).

6.90 The Pre-PBAC Response proposed that no additional net cost to the government was expected from the listing of periNIVO, and therefore changes to the current RSA cap for NSCLC immunotherapy was likely not required.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of nivolumab for the perioperative treatment of patients with resectable non-small cell lung cancer (NSCLC). The PBAC noted the perioperative use of nivolumab consisted of up to 4 doses prior to surgery in combination with chemotherapy (neoadjuvant treatment) and up to 12 months of treatment post-surgery as monotherapy (adjuvant treatment). The PBAC considered the appropriate comparator was neoadjuvant nivolumab (up to 3 doses prior to surgery in combination with chemotherapy) which is currently PBS listed. The PBAC considered that the additional doses of nivolumab in the adjuvant setting provided no clear clinical benefit compared to the comparator, however led to inferior safety and increased treatment burden for patients.

7.2 The primary reason for this outcome was due to the comparative clinical evidence.

7.3 The PBAC noted consumer comments from an individual, Rare Cancers Australia, Lung Foundation Australia, and the Medical Oncology Group of Australia (MOGA), which highlighted the need for new and effective treatment options for patients with resectable NSCLC. The PBAC noted the input emphasised the toxicity associated with current therapy options and nivolumab, and the high emotional and financial burden associated with this condition.

7.4 The PBAC considered there was a moderate clinical need for new and effective therapies for this patient group, noting that resectable NSCLC is a life-threatening condition and PBS-listed neoadjuvant/ adjuvant therapies only being moderately effective. The PBAC noted that there remained a number of PBS-listed therapies also available for patients with metastatic NSCLC. The PBAC noted that the additional doses of nivolumab in the adjuvant setting was not strongly supported in clinical guidelines[10].

[10] https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450 (v11.2024)

7.5 The PBAC considered that neoadjuvant nivolumab (neoNIVO) would be the therapy most likely to be replaced by periNIVO, making it the most appropriate main comparator.

7.6 The PBAC noted the clinical evidence for periNIVO was based on the CheckMate77T (CM77T) study, a direct, randomised, double-blind trial (n=461) comparing periNIVO (360 mg nivolumab every 3 weeks for a maximum of four cycles plus platinum-doublet chemotherapy, followed by surgery, followed by 480 mg nivolumab every 4 weeks for a maximum of 13 cycles) with neoadjuvant chemotherapy (neoChemo) (platinum-doublet every 3 weeks for a maximum of four cycles, followed by surgery). The PBAC noted 62% of patients were treated with adjuvant nivolumab. The PBAC noted that based on a median follow up of 25.4 months, periNIVO was associated with a statistically significant improvement in event free survival (EFS) compared with neoCHEMO (HR = 0.58, 95% CI: 0.42, 0.81), based on 76/229 (33.2%) events in the periNIVO arm and 113/232 (48.7%) events in the neoChemo arm. The PBAC noted that overall survival (OS) data was not available.

7.7 The PBAC noted that for the main comparator (neoNIVO) the submission's evidence was based on an adjusted (Bucher) indirect treatment comparison (ITC) of periNIVO in the CM77T clinical trial with neoNIVO in the CheckMate816 (CM816) clinical trial, using neoChemo as the common reference. The PBAC noted that the ITC of periNIVO versus neoNIVO was associated with a high level of uncertainty due to transitivity issues related to unadjusted differences in study design, patient clinical characteristics and demographics (paragraph 6.45). The PBAC also noted that the results from the ITC (event free survival [EFS] hazard ratio [HR]=0.92; 95% confidence interval [CI]: 0.59, 1.44) were associated with wide confidence intervals, indicating a high level of uncertainty around the estimated effect size. The PBAC considered that it was not possible to draw a reliable conclusion on the comparative effectiveness of periNIVO versus neoNIVO based on the presented Bucher adjusted ITC; however, on the basis of the evidence provided there was no clear clinical benefit compared to the comparator.

7.8 The PBAC noted that an additional ITC of periNIVO versus neoNIVO using patient-level data from CM77T and CM816 (Forde et al 2024[11]) had been provided in the PSCR (with additional information provided in the pre-PBAC response) which adjusted for baseline demographics and disease characteristics between study populations. The PBAC noted that the EFS HRs for the average treatment effect (ATE) and average treatment effect for the treated (ATT) analyses were 0.61 (95% CI: 0.39−0.97) and 0.59 (95% CI 0.38−0.92) respectively, which were more optimistic that the HR presented in the submission using the Bucher approach. The PBAC noted that the periNIVO group had been limited to those who had received at least one dose of adjuvant nivolumab, while the neoNIVO group consisted of all participants. The PBAC agreed with the ESC

[11] Forde, P., Peters, S., Doninton, J., Meadows-Shroshire, S., Tran, P., Lucherini, S., Erdmannm C., Sun, H., Cascone, T. 2024. Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816. World Conference on Lung Cancer. September 7-10; San Diego, SA, USA. Presentation number 3589.

that the exclusion of patients not receiving adjuvant nivolumab from the periNIVO arm likely biased the results in favour of CM77T, as patients in that trial who did not respond to or tolerate neoadjuvant nivolumab were excluded from the comparison. For this reason, the PBAC considered that the results from Forde 2024 were unlikely to be a reliable basis to support a claim of superior efficacy of periNIVO versus neoNIVO. Additionally, the PBAC noted the data was only available as a poster and the analysis had not been evaluated.

7.9 Overall, the PBAC considered the clinical data presented did not support the clinical claim of 'at least noninferior, and potentially superior' efficacy of periNIVO compared to neoNIVO.

7.10 The PBAC noted the submission provided data from a more recent CM816 4-year update of OS, and that there was a trend in favour of neoNIVO arm compared to neoChemo (HR = 0.71 [95% CI 0.47, 1.07]: p=0.0451). The PBAC noted that the stopping boundary for declaring statistical significance (0.0164) had not been crossed and therefore statistically significant differences in OS could not be claimed. As noted in paragraph 7.6, there is no OS data available for CM77T.

7.11 The PBAC considered that the claim of noninferior safety between periNIVO and neoNIVO was not supported by the data given that a higher proportion of patients treated with periNIVO in CM77T experienced any adverse events (AEs) (all-causality) compared with patients treated with neoNIVO in CM816 (50% versus 43%, respectively). In addition, the proportion of patients that experienced any AEs resulting in treatment discontinuation (all-causality) in the periNIVO arm in CM77T was more than double that of the neoNIVO arm in CM816 (25% versus 10%; relative risk [RR]=2.3 [95% CI 1.1, 2.9: p<0.001]).

7.12 The PBAC noted that the PSCR presented a cost-minimisation for the comparison of periNIVO versus neoNIVO. The PBAC considered that the proposed equi-effective doses were likely appropriate. The PBAC noted that the updated CMA provided in the pre-PBAC Response included Q2W dosing for periNIVO, which was also considered appropriate. The PBAC noted that the revised CMA incorporated the cost of Grade 3/4 AEs that were reported in ≥2% of patients in either the periNIVO arm of CM77T or the neoNIVO arm of CM816. However, the adverse event costs for perioperative nivolumab plus neoadjuvant chemotherapy were calculated to be lower per patient course of treatment compared to neoadjuvant nivolumab plus chemotherapy patients and considered that this was not aligned with the inferior safety profile of periNIVO versus neoNIVO. The PBAC also noted that incorrect methodology had been adopted to calculate the cost-minimised price of periNIVO in the CMA (see paragraph 6.73), and that a lower price would be required for the overall cost of periNIVO to be the same as neoNIVO. However, the PBAC advised that given the assumption of noninferiority, in terms of both effectiveness and safety, had not been adequately justified by the submission a cost-minimisation approach could not be accepted.

7.13 The PBAC noted that revised financial estimates with an updated price and substitution for neoNIVO was provided in the Pre-PBAC Response. The PBAC

considered the reduced uptake rate (%) adopted for Years 1−6 was likely reasonable. However, the PBAC noted that the revised financial model estimated that the net cost to the PBS/RPBS of listing of periNIVO would cost over $100 million in the first 6 years of listing. The PBAC noted that this large incremental cost was primarily due to an incorrect cost-minimised price for periNIVO.

7.14 The PBAC considered that in the absence of clinical evidence of an incremental clinical benefit associated with periNIVO versus neoNIVO, the increased resource requirements for administration in cancer units and increased patient treatment burden (with additional time toxicity[12] and adverse event toxicity) was not justified. However, the PBAC stated that it would reconsider its recommendation if new evidence, particularly in terms of a clinically meaningful improvement in OS, supporting the additional doses of nivolumab in the adjuvant setting, becomes available.

7.15 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.

[12] Gupta A, Eisenhauer EA and Booth CM. The time toxicity of cancer treatment. Journal of Clinical Oncology; 40 (15): 1611-1615