NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6310]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6310]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Bristol-Myers Squibb Pharmaceuticals Ltd:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response part 1
   b. Clarification response part 2
   c. Clarification responses A8

3. **Patient group, professional group, and NHS organisation submission** from:
   a. British Thoracic Oncology Group

4. **External Assessment Report** prepared by BMJ Technology Assessment Group
   a. Addendum

5. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost comparison appraisal

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non–small cell lung cancer [ID6310]

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
ID6310 Nivolumab perioperative NSCLC Document B [CON]	1.0	Yes	22 April 2025

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Contents

B.1 Decision problem, description of the technology, and clinical care pathway 6

B.1.1 Decision problem 6

B.1.2 Description of the technology being evaluated 11

B.1.3 Health condition and position of the technology in the treatment pathway 12

B.1.3.1 Background to the health condition 12

B.1.3.2 Mortality and survival 13

B.1.3.3 Morbidity 15

B.1.3.4 Positioning of perioperative nivolumab in the care pathway 15

B.1.4 Equality considerations 16

B.2 Key drivers of the cost-effectiveness of the comparator(s) 17

B.2.1 Clinical outcomes and measures 17

B.2.2 Resource use assumptions 19

B.3 Clinical effectiveness 20

B.3.1 Identification and selection of relevant studies 20

B.3.2 List of relevant clinical effectiveness evidence 20

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence 25

B.3.3.1 CheckMate-77T 25

B.3.3.2 NADIM-II 31

B.3.4 Critical appraisal of the relevant clinical effectiveness evidence 36

B.3.5 Clinical effectiveness results 37

B.3.5.1 CheckMate-77T 37

B.3.5.2 NADIM-II 47

B.3.6 Subgroup analysis 49

B.3.7 Meta-analysis 49

B.3.8 Indirect and mixed treatment comparisons 49

B.3.8.1 Traditional Bayesian network meta-analysis 50

B.3.8.2 Fractional polynomial network meta-analysis 50

B.3.8.3 Multilevel network meta-regression 52

B.3.8.4 Uncertainties in the indirect and mixed treatment comparisons 56

B.3.9 Adverse reactions 56

B.3.9.1 CheckMate-77T 56

B.3.9.2 NADIM-II 57

B.3.10 Conclusions about comparable health benefits and safety 58

B.3.11 Ongoing studies 59

B.4 Cost comparison analysis 60

B.4.1 Changes in service provision and management 60

B.4.2 Cost comparison analysis inputs and assumptions 61

B.4.2.1 Features of the cost comparison analysis 61

B.4.2.2 Intervention and comparators' acquisition costs 61

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B.4.2.3 Intervention and comparators' healthcare resource use and associated costs 63
B.4.2.4 Adverse reaction unit costs and resource use 66
B.4.2.5 Miscellaneous unit costs and resource use 66
B.4.2.6 Clinical expert validation 66
B.4.2.7 Uncertainties in the inputs and assumptions 66
B.4.3 Base-case results 66
B.4.4 Sensitivity and scenario analyses 66
B.4.5 Subgroup analysis 66
B.4.6 Interpretation and conclusions of economic evidence 67
B.5 References 68

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TABLES

Table 1. The decision problem 7
Table 2. Technology being evaluated 11
Table 3. Clinical outcomes and measures appraised in published NICE guidance for the comparator, perioperative pembrolizumab 18
Table 4. Clinical effectiveness evidence 21
Table 5. CheckMate-77T: summary of trial methodology 27
Table 6. CheckMate-77T: baseline characteristics of patients 30
Table 7. NADIM-II: summary of trial methodology 32
Table 8. NADIM-II: demographic and clinical characteristics of the patients at baseline (ITT population)[a] 35
Table 9. Quality assessment 37
Table 10. CheckMate-77T: event-free survival per BICR (primary endpoint): all randomly assigned patients (ITT population) 38
Table 11. CheckMate-77T: overall survival—all randomly assigned patients (ITT population) 39
Table 12. CheckMate-77T: pathological complete response (per BIPR) and major pathological response (per BIPR)–all randomly assigned patients (ITT population) 41
Table 13. CheckMate-77T: objective response rate and best overall response: all randomly assigned patients (ITT population) 42
Table 14. CheckMate-77T: time to death or distant metastasis per investigator—all randomly assigned patients (ITT population) 43
Table 15. CheckMate-77T: event-free survival 2 per investigator—all randomly assigned patients (ITT population) 45
Table 16. Summary of the trials used to carry out the indirect treatment comparison 50
Table 17. Event-free survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the fractional polynomial network meta-analysis 51
Table 18. Overall survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the fractional polynomial network meta-analysis 52
Table 19. Key baseline characteristics across the network of evidence informing the multilevel network meta-regression by study 53
Table 20. Event-free survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the multilevel network meta-regression 53
Table 21. Overall survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the multilevel network meta-regression 54

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Table 22. Results across sensitivity analyses: hazard ratios for periadjuvant nivolumab + neoadjuvant chemotherapy versus periadjuvant pembrolizumab + neoadjuvant chemotherapy event-free survival 55
Table 23. Safety profile 57
Table 24. Adverse events that occurred during neoadjuvant treatment 58
Table 25. Acquisition costs of the perioperative nivolumab and perioperative pembrolizumab 62
Table 26. Resource costs of the intervention and comparator technologies 64
Table 27. Base-case results 66

FIGURES

Figure 1. Kaplan-Meier survival curves by disease stage in people with lung cancer diagnosed in England in 2022 14
Figure 2. Lung cancer 1-year rate by stage in England 15
Figure 3. Potential position of perioperative nivolumab in the treatment pathway for resectable NSCLC in clinical practice in England and Wales 16
Figure 4. CheckMate-77T: study design 26
Figure 5. CONSORT patient flow diagram 29
Figure 6. NADIM-II: study design 32
Figure 7. NADIM-II: CONSORT patient flow diagram 34
Figure 8. CheckMate-77T: event-free survival per BICR, primary definition: all randomly assigned patients (ITT population) 38
Figure 9. CheckMate-77T: overall survival—all randomly assigned patients (ITT population) 40
Figure 10. CheckMate-77T: pathological complete response and major pathological response 42
Figure 11. CheckMate-77T: time to death or distant metastasis per investigator—all randomly assigned patients (ITT population) 44
Figure 12. CheckMate-77T: event-free survival on next line of therapy (EFS2)—all randomly assigned participants in the global population 45
Figure 13. CheckMate-77T: time to definitive deterioration in EQ-5D-3L visual analogue score (overall self-rated health status)—all randomly assigned patients 46
Figure 14. NADIM-II: pathological complete response per BICR (ITT population) 47
Figure 15. NADIM-II: progression-free survival per BICR (ITT population) 48
Figure 16. NADIM-II: Kaplan-Meier curve for progression-free survival (ITT population) 49

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B.1 Decision problem, description of the technology, and clinical care pathway

B.1.1 Decision problem

This submission covers the technology's full Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for this indication:

> "Nivolumab, in combination with platinum-based chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgical resection for the treatment of adults with resectable (tumours ≥ 4 cm or node positive) non–small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements."

Neoadjuvant followed by adjuvant treatment is referred to as "perioperative" treatment throughout this document.

The decision problem is summarised in Table 1.

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Table 1. The decision problem

	Final scope issued by NICE[1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with resectable non–small cell lung cancer (NSCLC)	People with resectable NSCLC	NA
Intervention	Nivolumab with chemotherapy for neoadjuvant treatment then nivolumab monotherapy for adjuvant treatment	Nivolumab with chemotherapy for neoadjuvant treatment then nivolumab monotherapy for adjuvant treatment	NA
Comparator(s)	▪ Neoadjuvant pembrolizumab (with chemotherapy) then adjuvant pembrolizumab monotherapy ▪ Neoadjuvant durvalumab (with chemotherapy) then adjuvant durvalumab monotherapy	▪ Neoadjuvant pembrolizumab (with chemotherapy) then adjuvant pembrolizumab monotherapy	BMS consider pembrolizumab to be the new SOC treatment for patients with resectable NSCLC in England, and thus believe that the most relevant comparator for cost comparison decision-making is perioperative pembrolizumab, for the following reasons: [redacted]

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	Final scope issued by NICE[1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			[redacted] ▪ Nivolumab and pembrolizumab have the same mechanism of action—both are PD-1 inhibitors, whereas durvalumab is a PD-L1 inhibitor. ▪ An indirect treatment comparison of nivolumab and pembrolizumab demonstrates a similar EFS and OS treatment effect between nivolumab and pembrolizumab, which supports the similarity in clinical trial results for perioperative nivolumab (CheckMate-77T) and perioperative pembrolizumab (KEYNOTE-671) (See Section B.3.8 and Appendix D.)
Outcomes	The outcome measures to be considered include: ▪ EFS ▪ pCR ▪ Response rates ▪ OS ▪ Adverse effects of treatment	The outcome measures considered include: ▪ EFS ▪ pCR ▪ Response rates ▪ OS ▪ Adverse effects of treatment	NA

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	Final scope issued by NICE[1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	▪ Health-related quality of life	▪ Health-related quality of life	
Economic analysis	This technology has been selected to be appraised as a cost comparison. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	BMS present a cost comparison analysis comparing the drug and administration costs of perioperative nivolumab versus perioperative pembrolizumab for a full course of treatment. All other costs are anticipated to be the same.	NA
Subgroups to be considered	If the evidence allows, subgroups will be considered based on: ▪ Whether nivolumab is used before and after surgery ▪ PD-L1 tumour proportion score ▪ Disease stage ▪ Presence of biological or genetic markers ▪ Histology (squamous vs. non-squamous)	BMS do not explore subgroup analyses for in this submission.	BMS seek reimbursement for the ITT population of the CheckMate-77T trial in line with the MHRA licence[4] and in line with TA1017[2] reimbursement. A significant patient benefit was observed in the primary analysis population of the CheckMate-77T trial, with a statistically significant and clinically relevant improvement in EFS compared with chemotherapy alone (HR, [redacted] 95% CI[redacted]).[5]

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	Final scope issued by NICE[1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	There are no anticipated equity or equality issues associated with this appraisal.	NA

BMS = Bristol Myers Squibb; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; ITT = intention to treat; MHRA = Medicines and Healthcare Products Regulatory Agency; NA = not assessed; NHS = National Health Service; OS = overall survival; pCR = pathological complete response; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death-ligand 1; SOC = standard of care; UK = United Kingdom.

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B.1.2 Description of the technology being evaluated

As summarised in Section B.1.1, this appraisal is for nivolumab as perioperative treatment (that is, neoadjuvant nivolumab + chemotherapy, followed by adjuvant nivolumab monotherapy) indicated for adults with resectable (tumours ≥ 4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.

Perioperative nivolumab has been compared against neoadjuvant chemotherapy (that is, neoadjuvant chemotherapy + placebo, followed by adjuvant placebo) in the CheckMate-77T clinical trial in adults with resectable stage II-IIIB[i] NSCLC (Table 2).[6]

Table 2. Technology being evaluated

UK approved name and brand name	Nivolumab (Opdivo®)
Mechanism of action	Nivolumab is a fully human, immunoglobulin type 4, PD-1 receptor-blocking monoclonal antibody that potentiates T-cell responses, including the ability of T cells to attack the tumour.[7,8] Nivolumab binds to PD-1 receptors on T cells with high affinity[7] and selectively disrupts inhibitory signalling triggered by PD-L1 and PD-L2, thereby restoring normal T-cell antitumour function. Expression of PD-1 is increased on immune cells in people with several types of cancer.[9,10]
Marketing authorisation/CE mark status	The MHRA approved nivolumab for use in the United Kingdom in this indication on 27 February 2025.[4]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	MHRA indication wording is: "Neoadjuvant and adjuvant treatment of NSCLC. OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgical resection, is indicated for the treatment of adults with resectable (tumours ≥ 4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements." Nivolumab (OPDIVO) also has MHRA regulatory approval for the management of the following conditions[4]: ▪ NSCLC ▪ Melanoma ▪ Malignant pleural mesothelioma (MPM) ▪ Renal cell carcinoma (RCC) ▪ Classical Hodgkin lymphoma (cHL) ▪ Squamous cell cancer of the head and neck (SCCHN) ▪ Urothelial carcinoma ▪ Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC) ▪ Oesophageal squamous cell carcinoma (OSCC) ▪ Oesophageal or gastro-oesophageal junction cancer (OC or GEJC) ▪ Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma

[i] Staging defined using American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 8th edition.

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Method of administration and dosage	Nivolumab is administered as an intravenous infusion at a dosage of 360 mg every 3 weeks + chemotherapy every 3 weeks for up to 4 cycles as neoadjuvant treatment, followed by surgery, and then administered as an intravenous infusion at a dosage of 480 mg every 4 weeks for up to 13 cycles (approximately 1 year) as adjuvant therapy after surgery.
Additional tests or investigations	No additional tests or investigations outside current practice are expected.
List price and average cost of a course of treatment	▪ Nivolumab list price per dose: £439 per vial ▪ Chemotherapy price per dose: dependent on combination ▪ Average cost of a course of treatment at list price: £84,288.00 (see Section B.4.3)
PAS/commercial arrangement (if applicable)	[redacted]

ALK = anaplastic lymphoma kinase; BMS = Bristol Myers Squibb; CE = cost-effectiveness; EGFR = epidermal growth factor receptor; MHRA = Medicines and Healthcare Products Regulatory Agency; NHSE = National Health Service England; PAS = patient access scheme; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death-ligand 1; PD-L2 = programmed cell death-ligand 2; SmPC = summary of product characteristics; UK = United Kingdom.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Background to the health condition

Lung cancer is the most common cancer worldwide, and is the leading cause of cancer deaths, both worldwide and in the United Kingdom (UK).[12-14] According to National Lung Cancer Audit data from England in 2022[15]:

- Approximately 36,886 people were diagnosed with lung cancer[15]
  - Of these, approximately 90% were known or assumed to have NSCLC.

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- Approximately 55% of all people with lung cancers were diagnosed with early or locally advanced lung cancer (stage I-III of the 8th AJCC/UICC tumour-node-metastasis [TNM] staging system[ii]),[15] making them potentially eligible for surgical resection. Note, of the stage III non-metastatic patients, approximately 50% are resectable, although that proportion is increasing over time as borderline cases are pushed to a curative setting.[17]

Treatment options for those with resectable NSCLC are typically given with curative intent. Such treatment increases the time a patient survives without an event occurring (event-free survival [EFS]). However, the disease recurs in a substantial proportion of people (30%-55%) after surgery, presenting as distant metastases or locoregional metastases.[18]

Disease recurrence can happen rapidly: 50%-90% of recurrence presents within 2 years after surgery and 90%-95% within 5 years. Furthermore, the risk of recurrence is proportional to stage: patients with higher disease stage are at increased risk of relapse.[19]

B.1.3.2 Mortality and survival

According to the National Lung Cancer Audit data from England in 2022, median overall survival (OS) of people with lung cancer was 327 days, and median OS decreased with increasing stage at diagnosis (Figure 1).[15] Data specific to NSCLC are not available for England or the UK; therefore, overall lung cancer statistics are presented.

[ii] The 8th edition of the AJCC/UICC staging system for NSCLC is used when referring to staging in this document.[16] Stages IA, IB, IIA, and IIB are considered early disease. Stages IIIA, IIIB, IIIC are considered locally advanced disease, and Stages IVA and IVB are considered metastatic disease.
The CheckMate-77T trial for perioperative nivolumab described in Section B.3.2 of this submission is based on this staging system and includes patients with stages IIA-IIIB NSCLC.

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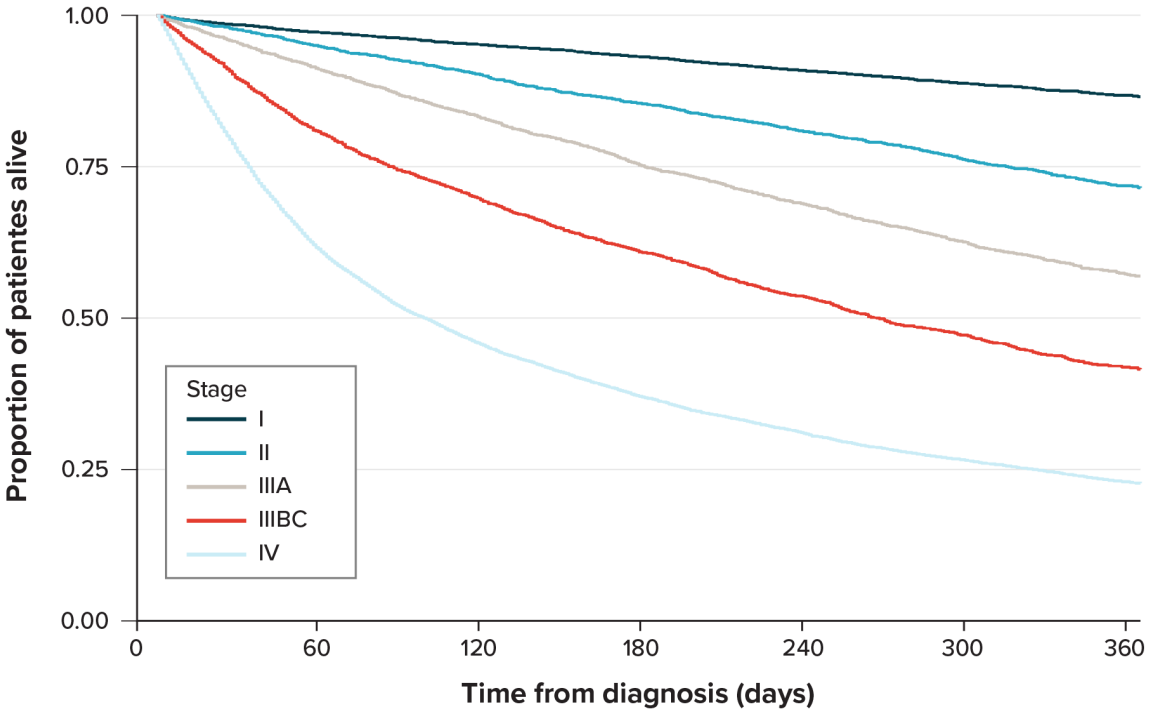
Figure 1. Kaplan-Meier survival curves by disease stage in people with lung cancer diagnosed in England in 2022



Source: NLCA (2024)[15]

Both the 1-year and 5-year survival rates for lung cancer in England decreased with increasing stage (2016-2020 data) (Figure 2).[20] The overall 1-year relative survival rate for lung cancer in 2022 was 48% in England.[15] Five-year relative survival for lung cancer is generally below the European average in the UK.[21]

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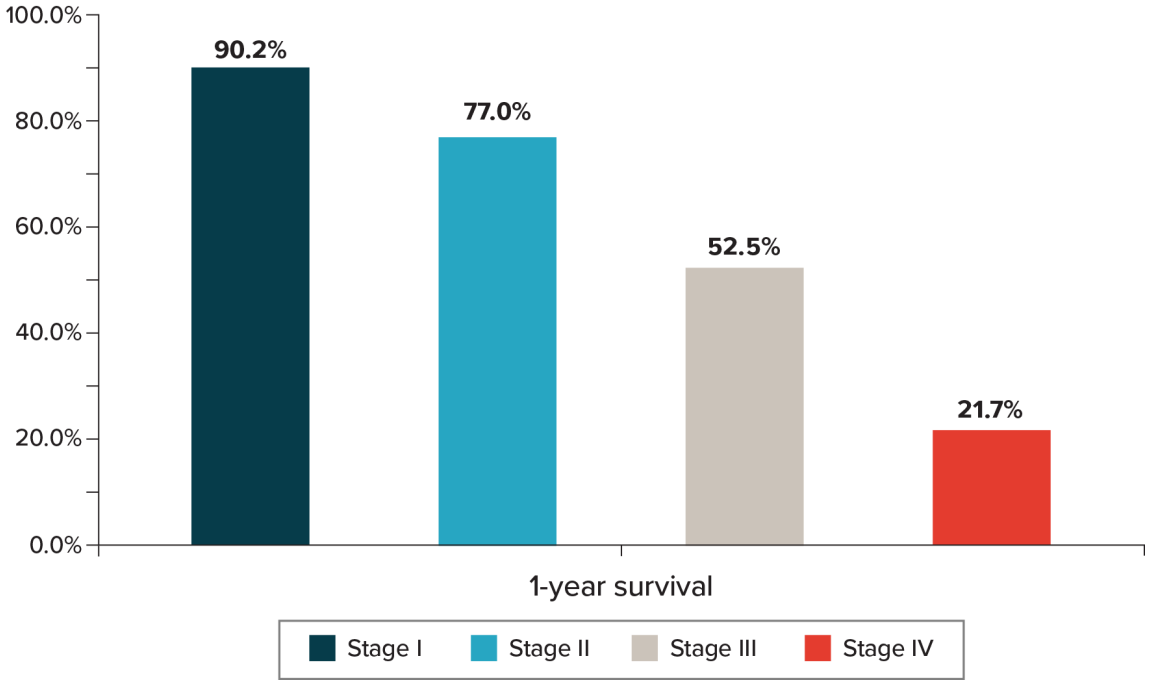
Figure 2. Lung cancer 1-year rate by stage in England



Source: Cancer Research UK (2024)[20]

An unmet need exists for treatment options to reduce the risk of recurrence and improve survival for those with stage I-III NSCLC.

B.1.3.3 Morbidity

For people with resectable NSCLC, fatigue, dyspnoea, pain, and cough are the most troublesome symptoms that negatively impact health-related quality of life (HRQOL).[22-24]

In advanced NSCLC, after locoregional or distant metastatic recurrence, HRQOL is further reduced and worsening symptoms are experienced.[25] Notably, bone metastases (occurring in approximately 40% of people with lung cancer) and brain metastases (occurring in approximately 50% of people with NSCLC)[26] are associated with specific debilitating symptoms, such as bone pain, risk of fracture, headache, seizures, and other neurological complications, all of which substantially impact HRQOL.[27-31] Therefore, optimising systemic treatment for resectable tumours is important to extend survival and prevent the worsening of symptoms and deterioration of HRQOL, which occur during disease progression.

NSCLC does not only affect the patient. Caregivers for people with NSCLC also experience a considerable burden associated with care.[32,33] Improved treatment options, may, therefore help to reduce the negative HRQOL impact on people with NSCLC, as well as reduce the burden on their caregivers.

B.1.3.4 Positioning of perioperative nivolumab in the care pathway

NICE-recommended treatment options for people with newly diagnosed resectable NSCLC include immunotherapy, surgery, radiotherapy, chemotherapy, or a combination of these.[34]

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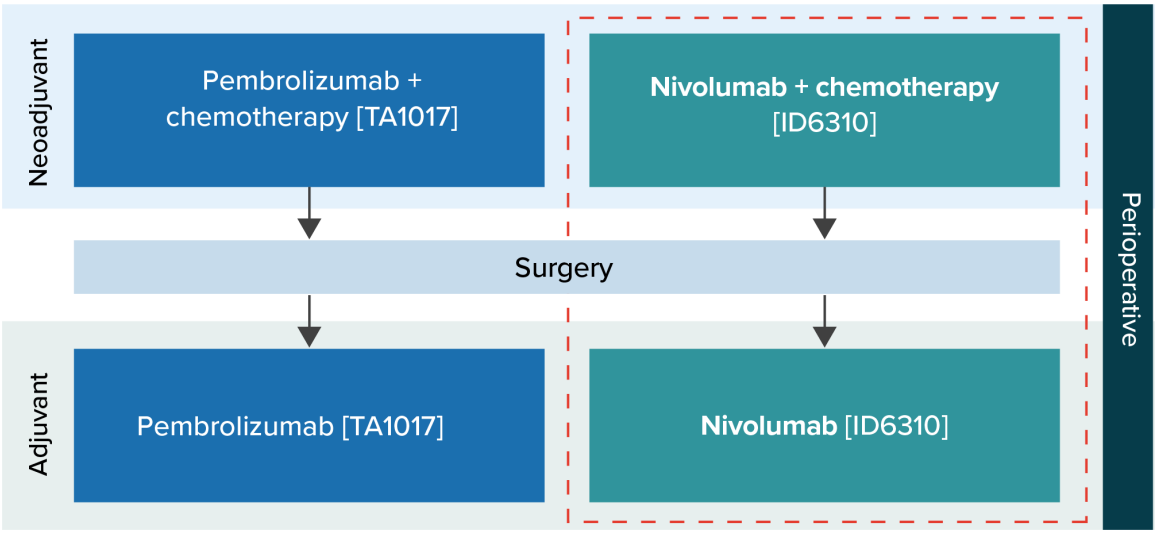
Of note, immunotherapy is not typically offered to people with NSCLC who carry certain driver mutations or biomarkers; instead, targeted treatment is offered. Therefore, these targeted treatments are not relevant comparators for this appraisal. For example, people who carry an ALK biomarker are treated with adjuvant alectinib, and people with an EGFR biomarker are treated with adjuvant osimertinib.[34]

Perioperative treatments are suitable for a wide range of people with resectable NSCLC and are not further restricted by disease stage. Perioperative pembrolizumab recently became the standard of care (SOC) for people with resectable NSCLC in England, following a positive recommendation by NICE in 2024,[2] [redacted] Considering the above evidence, Bristol Myers Squibb (BMS) believe that perioperative pembrolizumab represents the new SOC treatment for patients with resectable NSCLC.

Perioperative nivolumab will be an additional perioperative treatment option available for patients with resectable NSCLC with no ALK or EGFR mutations, offering very similar benefits to patients as perioperative pembrolizumab (Figure 3). Perioperative nivolumab has the same mechanism of action as pembrolizumab; both are programmed cell death protein 1 (PD-1) inhibitors, and nivolumab is already familiar to clinicians in this early NSCLC setting following its recommendation in 2023 as neoadjuvant therapy.[3]

Figure 3. Potential position of perioperative nivolumab in the treatment pathway for resectable NSCLC in clinical practice in England and Wales



NSCLC = non–small cell lung cancer.

Sources: NICE (2024)[2]; NICE (2025)[35]

B.1.4 Equality considerations

No equality issues are foreseen.

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B.2 Key drivers of the cost-effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

The clinical endpoints from the CheckMate-77T clinical trial, used in this submission, are the same as those used in the NICE evaluation of perioperative pembrolizumab.[2]

Endpoints include:

- EFS
- Pathological complete response (pCR)
- Major pathological response (MPR)
- OS
- Adverse events (AEs)
- HRQOL

In the pembrolizumab TA1017 submission, EFS was accepted as an appropriate primary outcome in the perioperative setting (Table 3).

The main driver of the cost-effectiveness of perioperative pembrolizumab, in the economic model submitted for TA1017, is the delayed rate of disease recurrence (and therefore longer time in EFS) associated with pembrolizumab relative to comparator treatments. This improved relative time in EFS improves the cost-effectiveness of pembrolizumab as EFS is associated with improved morbidity and mortality compared with other health states like locoregional or distant metastatic NSCLC. This increased time in EFS accumulates more quality-adjusted life-years (QALYs) for pembrolizumab compared with comparator treatments. Although pembrolizumab may be more costly than other comparator treatments, the additional QALYs generated by pembrolizumab meant that the NICE committee determined perioperative pembrolizumab to be a cost-effective use of NHSE resources.

The clinical benefit of perioperative nivolumab should be considered comparable to perioperative pembrolizumab as described above; the indirect treatment comparison (ITC) between perioperative nivolumab and perioperative pembrolizumab supports this conclusion (Section B.3.8).

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Table 3. Clinical outcomes and measures appraised in published NICE guidance for the comparator, perioperative pembrolizumab

Appraisal	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER[a]	Committee's preferred assumptions	Uncertainties
NICE TA1017	EFS	Time from randomisation until radiographic disease progression, local progression precluding surgery, inability to resect the tumour, local or distant recurrence, or death due to any cause	Yes. Key driver of cost-effectiveness.	Increased time in EFS for pembrolizumab patients led to ICER decrease. The ICER was highly sensitive to changes in this outcome.	The committee agreed that using EFS as a surrogate for OS in the model was acceptable. The committee also agreed that the modelling approach of censoring EFS events to create individual curves for transitions from event free to local recurrence/progression, distant metastasis and death was appropriate for decision-making.	The committee noted that the transition out of the EF state had a large influence in the QALYs estimated in the model and were based on relatively immature data. The committee also noted the uncertainty around the duration of treatment effect and the modelling of cure. It concluded that in the absence of more mature evidence that would have reduced the uncertainty around transitions out of the EF state, the modelling approach was suitable for decision-making.

EF = event-free; EFS = event-free survival; ICER = incremental cost-effectiveness ratio; OS = overall survival.

[a] Was the ICER sensitive to changes in this outcome? How did changes in the outcome affect the ICER (increase or decrease)?

Source: NICE (2024)[2]

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B.2.2 Resource use assumptions

Pembrolizumab and nivolumab have the same mechanism of action, similar trial designs, similar ITC results, and similar patient populations. As a result, the resource use for perioperative nivolumab is anticipated to be sufficiently similar to that for pembrolizumab for costs of chemotherapy agents used in combination with the immuno-oncology agent, AEs, hospitalisations, healthcare appointments (outpatients, community nurse, clinical nurse specialists, general practitioner consultations), monitoring (computerised tomography [CT] chest scans, chest radiography, electrocardiograms, positron emission tomography with CT scans, magnetic resonance imaging scans), costs of subsequent therapy, and end-of-life costs.

The External Assessment Group (EAG) and committee accepted the resource use and cost estimates included in TA1017.[2] Therefore, only the acquisition costs of nivolumab and pembrolizumab and their administration (such as the number of healthcare appointments needed) are expected to differ.

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B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken according to a predefined protocol, and database searches were conducted on 16 November 2024 to identify randomised controlled trials (RCTs) relevant to the decision problem, assessing the comparative efficacy of treatments in resectable NSCLC. Considering the scope of this appraisal, results were limited to studies relating to the perioperative setting only.

See Appendix D for full details of the process and methods used to identify and select the clinical evidence.

B.3.2 List of relevant clinical effectiveness evidence

Two RCTs that evaluated nivolumab as perioperative therapy for the treatment of patients with NSCLC were identified in the SLR: CheckMate-77T (NCT04025879) and NADIM-II (NCT03838159) (Table 4).

CheckMate-77T is a phase 3, randomised, double-blind trial of perioperative nivolumab patients with resectable, stage IIA-IIIB NSCLC, and is the key study relevant to the decision problem described in Section B.1.1. NADIM-II is an open-label phase 2 trial of perioperative nivolumab in patients with resectable stage IIIA or IIIB NSCLC conducted in Spain.[36]

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Table 4. Clinical effectiveness evidence

Study	NCT04025879; Cascone et al. (2024)[6]; BMS data on file (2023)[37]	NCT03838159; Provencio et al. (2023)[36]
Study design	Phase 3, randomised, double-blind trial	Phase 2, open-label trial
Population	Patients with newly diagnosed, resectable, stage IIA-IIIB (AJCC/UICC 8th edition) NSCLC	Patients with newly diagnosed, resectable stage IIIA-IIIB (AJCC/UICC 8th edition) NSCLC
Intervention(s)	Nivolumab 360 mg administered as an intravenous injection every 3 weeks + SOC chemotherapy[a] for up to 4 cycles as neoadjuvant treatment followed by surgery, and then nivolumab 480 mg administered as an intravenous injection every 4 weeks for up to 13 cycles (approximately 1 year) as adjuvant therapy after surgery	Nivolumab 360 mg administered as an intravenous injection plus chemotherapy (paclitaxel 200 mg/m^2 BSA and carboplatin AUC 5 mg/mm/min) as neoadjuvant treatment every 3 weeks up to 3 cycles, followed by surgery; for patients with R0 resections only, nivolumab 480 mg once every 4 weeks for 6 months as adjuvant therapy after surgery
Comparator(s)	Placebo administered as an intravenous injection every 3 weeks + SOC chemotherapy[a] for up to 4 cycles as neoadjuvant therapy, followed by surgery, and then placebo every 4 weeks for up to 13 cycles (approximately 1 year) after surgery	Chemotherapy (paclitaxel 200 mg/m^2 BSA and carboplatin AUC 5 mg/mm/min) as neoadjuvant treatment every 3 weeks up to 3 cycles, followed by surgery, and then 3 observation visits after surgery
Indicate if study supports application for marketing authorisation (yes/no)	Yes	No
Reported outcomes specified in the decision problem	▪ EFS ▪ pCR ▪ Response rates (MPR, objective response rate) ▪ OS ▪ Safety ▪ HRQOL	▪ pCR ▪ PFS ▪ OS ▪ Response rates (MPR, overall response rate) ▪ Safety

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Study	NCT04025879; Cascone et al. (2024)[6]; BMS data on file (2023)[37]	NCT03838159; Provencio et al. (2023)[36]
All other reported outcomes	▪ TTDM ▪ EFS, MPR, and pCR by PD-L1 status ▪ Feasibility of surgery and rate of peri- and postoperative complications ▪ Physical function (PROMIS T-scores) ▪ Disease-related symptoms and impacts on HRQOL (FACT-L and NSCLC-SAQ scores) ▪ GP5 scores from the FACT-L ▪ NSCLC-SAQ scores ▪ PK ▪ EFS after next line of treatment (EFS2) ▪ Immunogenic potential of nivolumab (ADA) ▪ Biomarkers and their association with efficacy (gene expression signatures, driver mutations, peripheral markers, and soluble factors within blood and other factors within blood and their association with clinical outcomes, cell-free DNA for blood TMB and/or MRD analysis)	Not available
Summary of statistical analyses	The enrolment of 452 patients in the 2 treatment groups would provide the trial with 90% power to detect an HR of 0.65 with a two-sided type I error of 0.05, according to the observation of approximately 231 patients with disease progression or recurrence, abandoned surgery, or death. According to the protocol, the interim analysis was to be performed when 185 such events had occurred.[6] The first interim analysis for OS would be triggered at 140 events (80% of events; *P* value cutoff: ≤ 0.0237; critical HR, 0.682).[5] Efficacy was evaluated in all the patients who had undergone randomisation (ITT population), which was assessed in a time-to-event analysis from randomisation to disease progression or death from any cause. Data for patients who had received subsequent therapy before EFS review were censored at the last evaluable tumour assessment on or before the date that subsequent therapy had been initiated.	Based on the results of the NADIM trial, it was assumed that 10% of the patients in the chemotherapy group and 40% in the nivolumab group would have a pCR. Assuming that 15% of the patients would drop out of the trial, a sample size of 90 patients, randomly assigned in a 2:1 ratio was estimated to give the trial 80% power to detect a significant difference between groups, at an alpha level of 5%. An efficacy analysis was performed in the ITT population, including all patients who had undergone randomisation. The Kaplan-Meier method was used to estimate PFS and OS at 24 months. *P* values are two-sided.

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Study	NCT04025879; Cascone et al. (2024)[6]; BMS data on file (2023)[37]	NCT03838159; Provencio et al. (2023)[36]
	Stratified analyses were performed for main and supportive analyses of the efficacy outcomes, and unstratified analyses were performed for supplementary analyses of the efficacy outcomes. Safety was evaluated in patients who had received at least 1 dose of a trial treatment. A stratified two-sided log-rank test was used to compare differences in EFS between the treatment groups. The stratified Cochran–Mantel–Haenszel method was used to assess the pathological response, with CIs calculated by means of the Clopper–Pearson method.[6] A 97.36% CI was estimated for the primary analysis on the basis of the boundary for statistical significance ($P < 0.0264$). Other outcomes were not formally compared, standard 95% CIs are reported. Confidence intervals for outcomes that were not part of the hypothesis testing were not adjusted for multiplicity and were descriptive in nature.[6] To date, 3 database locks have occurred, as follows: ▪ Interim analysis 1 for EFS was the first planned interim analysis of the primary endpoint of EFS per BICR. As of the clinical data cutoff (26 July 2023), 189 EFS events (81.8% of the total number of EFS events) had occurred. The database lock was on 6 September 2023 (median follow-up, 25.4 months [15.7-44.2]). Considering a subsequent analysis was conducted for OS and EFS (see bullet below), only data for outcomes other than EFS and OS are presented here from this database lock. ▪ An additional database lock took place on 26 April 2024 (median follow-up [range]: 33.3 months [23.6-52.1]), which provided an updated analysis of EFS.[38] ▪ Interim analysis 1 for OS was the first planned interim analysis of OS and provides the latest analysis of EFS; this database lock occurred on 16 December 2024 and results for OS and EFS are presented here. This is considered the final analysis of EFS.	*P* values of less than 0.05 were considered to indicate statistical significance.

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Study	NCT04025879; Cascone et al. (2024)[6]; BMS data on file (2023)[37]	NCT03838159; Provencio et al. (2023)[36]
Critical appraisal of the study design	See Section B.3.4	See Section B.3.4

ADA = antidrug antibody; AJCC = American Joint Committee on Cancer; AUC = area under the curve; BICR = blinded independent central review; BSA = body surface area; CI = confidence interval; EFS = event-free survival; FACT-L = Functional Assessment of Cancer Therapy-Lung; HRQOL = health-related quality of life; ITT = intention to treat; MPR = major pathological response; MRD = minimal residual disease; NSCLC = non–small cell lung cancer; NSCLC-SAQ = Non–Small Cell Lung Cancer Symptom Assessment Questionnaire; OS = overall survival; pCR = pathological complete response; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; SOC = standard of care; TMB = tumour mutational burden; TTDM = time to death or distant metastases; UICC = Union for International Cancer Control.

[a] Squamous histology: carboplatin (AUC5 or AUC6) + paclitaxel (175 mg/m^2 or 200 mg/m^2); carboplatin (AUC5 or AUC6) + docetaxel (75 mg/m^2); cisplatin (75 mg/m^2) + docetaxel (75 mg/m^2); Non-squamous histology: carboplatin (AUC5 or AUC6) + pemetrexed (500 mg/m^2); cisplatin (75 mg/m^2) + pemetrexed (500 mg/m^2); carboplatin (AUC5 or AUC6) + paclitaxel (175 mg/m^2 or 200 mg/m^2).

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B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 CheckMate-77T

CheckMate-77T was a randomised, double-blind trial comparing neoadjuvant nivolumab + chemotherapy followed by adjuvant nivolumab, with neoadjuvant placebo + chemotherapy followed by adjuvant placebo, in newly diagnosed resectable (stage IIA [> 4 cm] to stage IIIB [T3N2 or T4N2]), AJCC/UICC 8th edition) NSCLC. See Section B.1.3.1 for a description of the AJCC/UICC staging system. Following the completion of neoadjuvant treatment, all participants who remain operative candidates were required to undergo definitive surgery for NSCLC within 6 weeks of the last neoadjuvant treatment administration.

Nivolumab was evaluated in a 360-mg flat dose with chemotherapy every 3 weeks for up to 4 cycles (neoadjuvant) followed by adjuvant nivolumab in a 480-mg flat dose every 4 weeks for up to 13 cycles (approximately 1 year) versus placebo alone (Figure 4). Table 5 outlines the trial methodology. Additional details of the statistical analyses and endpoints are provided in Section B.3.5.

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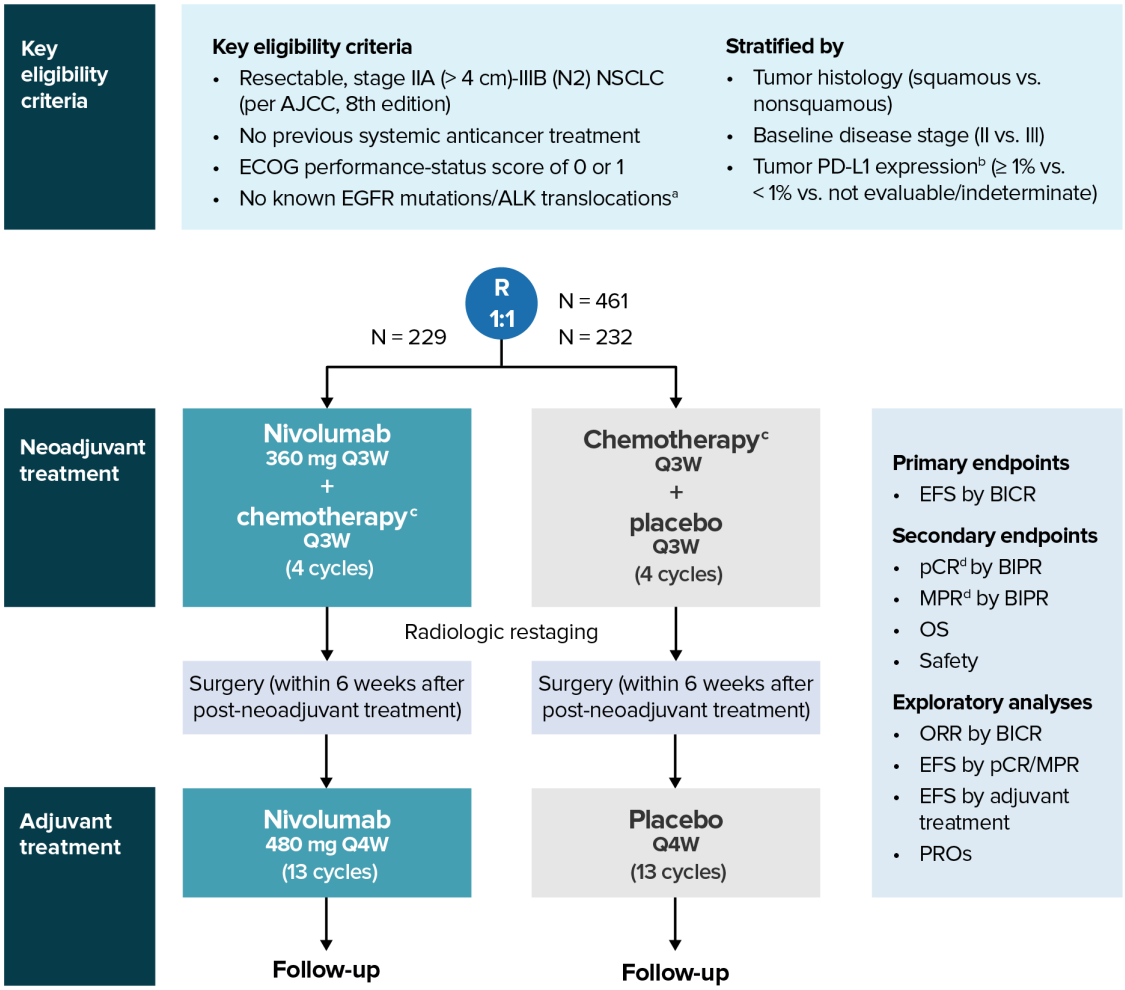
Figure 4. CheckMate-77T: study design



ALK = anaplastic lymphoma kinase; AJCC = American Joint Committee on Cancer; BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; MPR = major pathological response; ORR = objective response rate; OS = overall survival; pCR = pathological complete response; PD-L1 = programmed cell death-ligand 1; PRO = patient-reported outcome; Q4W = every 4 weeks.

[a] Testing for EGFR mutations was mandatory for all patients with non-squamous disease, and testing for ALK alterations was mandatory for all patients with a history of ALK alterations. EGFR and ALK testing were performed using the Food and Drug Administration (or local health authority)–approved assays.

[b] Tumour PD-L1 expression was determined by the PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako).

[c] Patients with squamous tumour histology received either cisplatin plus docetaxel or carboplatin plus paclitaxel. Patients with non-squamous tumour histology received either cisplatin plus pemetrexed, carboplatin plus pemetrexed, or carboplatin plus paclitaxel.

[d] pCR and MPR were assessed according to pan-tumour immune-related pathological response criteria.

Source: Cascone et al. (2024)[6]

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Table 5. CheckMate-77T: summary of trial methodology

Location	86 sites in 18 countries (Argentina, Australia, Belgium, Brazil, China, Czech Republic, France, Germany, Italy, Japan, Mexico, Netherlands, Poland, Romania, Russian Federation, Spain, Taiwan, the United States)	
Trial design	Randomised, double-blind, placebo-controlled, phase 3 trial	
Eligibility criteria for participants	Inclusion criteria: ▪ Males and females aged ≥ 18 years ▪ Histologically confirmed stage IIA > 4 cm) to IIIB (T3N2 or T4N2) non–small cell lung cancer (NSCLC) (according to AJCC 8th edition) with disease that is considered resectable ▪ Eligible for complete resection and must agree to undergo SOC surgery for complete resection of NSCLC after neoadjuvant therapy ▪ No prior systemic anticancer treatment for NSCLC ▪ ECOG PS of 0-1 ▪ Tissue from lung tumour to be available for biomarker testing	Key exclusion criteria: ▪ Patients who have received prior chemotherapy or any other cancer therapy for resectable NSCLC ▪ Patients with an active, known or suspected autoimmune disease ▪ Known EGFR mutations or ALK translocations ▪ Patients with grade ≥ 2 peripheral neuropathy ▪ Patients with brain metastases ▪ Patients with a condition requiring systemic treatment with immunosuppressive medications within 14 days of randomisation ▪ Patients with interstitial lung disease or active, non-infectious pneumonitis ▪ Patients with previous malignancies unless a complete remission ≥ 2 years prior to first treatment and no additional therapy required ▪ History of allergy or hypersensitivity to study drugs and their components
Settings and locations where the data were collected	See location	
Trial drugs **Permitted and disallowed concomitant medication**	▪ Neoadjuvant nivolumab + chemotherapy followed by adjuvant nivolumab (n = 229) – Neoadjuvant nivolumab at a flat dose of 360 mg as 30-minute IV infusion every 3 weeks for up to 4 cycles followed by adjuvant nivolumab at a flat dose of 480 mg as 30-minute IV infusion every 4 weeks for up to 13 cycles – Chemotherapy ▪ Squamous histology: – Carboplatin (AUC5 or AUC6) + paclitaxel (175 mg/m^2 or 200 mg/m^2) – Carboplatin (AUC5 or AUC6) + docetaxel (75 mg/m^2) – Cisplatin (75 mg/m^2) + docetaxel (75 mg/m^2) ▪ Non-squamous histology: – Carboplatin (AUC5 or AUC6) + pemetrexed (500 mg/m^2) – Cisplatin (75 mg/m^2) + pemetrexed (500 mg/m^2)	

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	– Carboplatin (AUC5 or AUC6) + paclitaxel (175 mg/m^2 or 200 mg/m^2) ▪ Neoadjuvant chemotherapy + placebo followed by placebo (n = 232) – The same chemotherapy regimens were available in the placebo arm ▪ Disallowed concomitant medication: immunosuppressive agents; immunosuppressive doses of systemic corticosteroids; any previous anticancer treatments; any additional, concurrent antineoplastic therapy; botanical preparations; live / attenuated vaccines. No prohibited therapies during the posttreatment follow-up phase.
Primary outcomes (including scoring methods and timings of assessments)	EFS: time from randomisation to any progression of disease precluding surgery, progression or recurrence of disease (per BICR using RECIST 1.1) after surgery, or death due to any cause. Patients who did not undergo surgery for reasons other than progression were considered to have an event at RECIST 1.1 progression or death.
Preplanned subgroups	▪ Tumour histology (squamous/non-squamous) ▪ NSCLC stage (II vs. III) ▪ PD-L1 status (≥ 1%/< 1%, indeterminate, or not evaluable)

AJCC = American Joint Committee on Cancer; ALK = anaplastic lymphoma kinase; AUC = area under the curve; BICR = blinded independent central review; ECOG PS = Eastern Cooperative Oncology Group performance status; EFS = event-free survival; EGFR = epidermal growth factor receptor; IV = intravenous; PD-L1 = programmed cell death-ligand 1; RECIST = Response Evaluation Criteria in Solid Tumours; SOC = standard of care.

Sources: Cascone et al. (2024)[6]; BMS data on file (2023)[37]; BMS data on file (2019)[39]

B.3.3.1.1 CheckMate-77T: patient disposition and baseline characteristics

Patient flow for the first planned interim analysis is presented in Figure 5.

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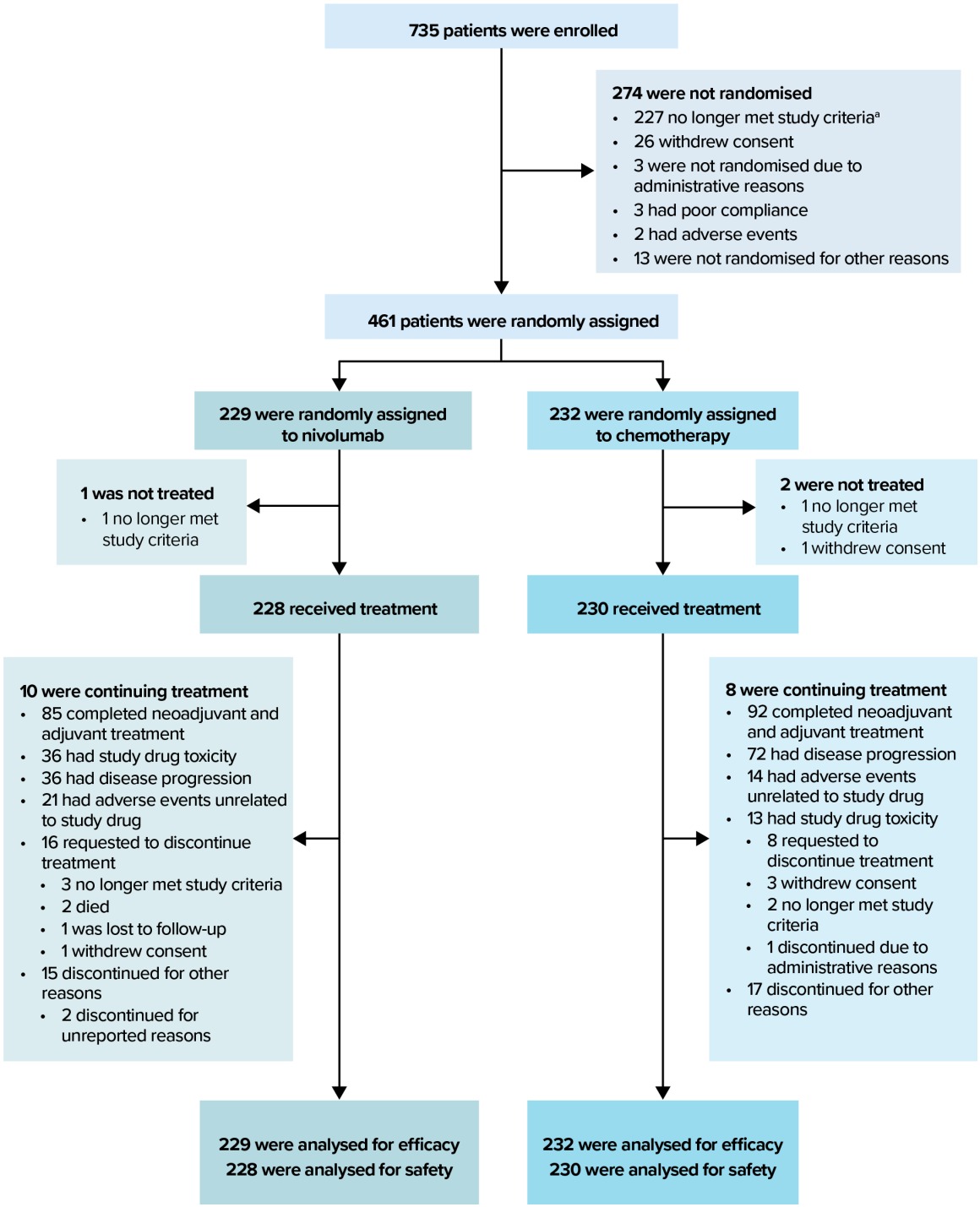
Figure 5. CONSORT patient flow diagram



NSCLC = non–small cell lung cancer.

[a] Reasons for no longer meeting study criteria included not having stage IIA (> 4 cm) to IIIB (T3N2 or T4N2) NSCLC, having metastases, having a tumour with a genetic mutation, or having an unresectable tumour.

Source: Cascone et al. (2024)[6]

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A total of 461 patients were randomly assigned (229 to the perioperative nivolumab group and 232 to the chemotherapy group). Patients had a median age of 66 years, and 73% were male.[6] Demographic and baseline characteristics of all randomly assigned patients in the 2 treatment arms were well balanced and were largely representative of those observed in the overall NSCLC population (Table 6).[6]

Table 6. CheckMate-77T: baseline characteristics of patients

Characteristic	Nivolumab (N = 229)	Chemotherapy (N = 232)
Age (years), median (range)	66.0 (37-83)	66.0 (35-86)
Male, n (%)	167 (72.9)	160 (69.0)
Race, n (%)[a]		
White	155 (67.7)	175 (75.4)
Black	4 (1.7)	4 (1.7)
Asian	66 (28.8)	50 (21.6)
Other	4 (1.7)	3 (1.3)
Geographic region, n (%)		
North America	23 (10.0)	21 (9.1)
Europe	123 (53.7)	127 (54.7)
Asia	65 (28.4)	50 (21.6)
Rest of the world [b]	18 (7.9)	34 (14.7)
ECOG PS [c]		
0	147 (64.2)	141 (60.8)
1	82 (35.8)	91 (39.2)
Disease stage, n (%) [d]		
IIA	15 (6.6)	18 (7.8)
IIB	66 (28.8)	63 (27.2)
IIIA	103 (45.0)	114 (49.1)
IIIB	43 (18.8)	35 (15.1)
Node stage, n (%)[e]		
N0	80 (34.9)	87 (37.5)
N1	56 (24.5)	52 (22.4)
N2	91 (39.7)	91 (39.2)
Single station	59 (25.8)	53 (22.8)
Multistation	31 (13.5)	38 (16.4)
Smoking status, %		
Never smoker	17 (7.4)	27 (11.6)
Current/former smoker	212 (92.6)	205 (88.4)
Histology, n (%)		
Squamous	116 (50.7)	118 (50.9)[f]
Non-squamous	113 (49.3)	114 (49.1)

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Characteristic	Nivolumab (N = 229)	Chemotherapy (N = 232)
Tumour PD-L1 expression		
< 1%	93 (40.6)	93 (40.1)
≥ 1%	128 (55.9)	128 (55.2)
1%-49%	83 (36.2)	76 (32.8)
≥ 50%	45 (19.7)	52 (22.4)
Not evaluable	8 (3.5)	11 (4.7)
Neoadjuvant platinum chemotherapy; n (%)[g]		
Cisplatin	55 (24.0)	42 (18.1)
Carboplatin	167 (72.9)	180 (77.6)

AJCC = American Joint Committee on Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; PD-L1 = programmed cell death-ligand 1.

[a] Race was reported by the patients.

[b] This category includes Argentina, Australia, Brazil, and Mexico.

[c] ECOG PS scores range from 0-5, with higher scores indicating greater disability.

[d] Data for disease stage are from case-report forms, with staging criteria of the AJCC Staging Manual, 8th edition, used for classification.

[e] N3 node stage was reported in 2 patients (0.9%) in each treatment group.

[f] One patient (0.4%) in the chemotherapy group with a squamous tumour had a reported *EGFR* mutation; this finding was tested locally and could not be confirmed because of site closure interval.

[g] Five patients (2.2%) in the nivolumab group and 6 patients (2.6%) in the chemotherapy group switched from cisplatin to carboplatin. Neoadjuvant platinum chemotherapy was not reported in 2 patients (0.9%) in the nivolumab group and 4 patients (1.7%) in the chemotherapy group.

Sources: Cascone et al. (2024)[6]; BMS data on file (2023)[37]

B.3.3.2 NADIM-II

NADIM-II was an open-label, multicentre, randomised, phase 2 trial comparing neoadjuvant nivolumab + chemotherapy with chemotherapy alone, followed by surgery in patients with resectable (according to the AJCC/UICC 8th edition) stage IIIA or IIIB NSCLC.[36] Following surgery, patients in the nivolumab group received adjuvant nivolumab for 6 months.

Nivolumab was evaluated in 360 mg flat dose with chemotherapy every 3 weeks for up to 3 cycles before surgery. Patients in the experimental group who had R0 resections (i.e., resection with no residual tumour cells visible on the margin) received adjuvant nivolumab in a 480-mg flat dose every 4 weeks for 6 months (Figure 6). Table 7 outlines the trial methodology.

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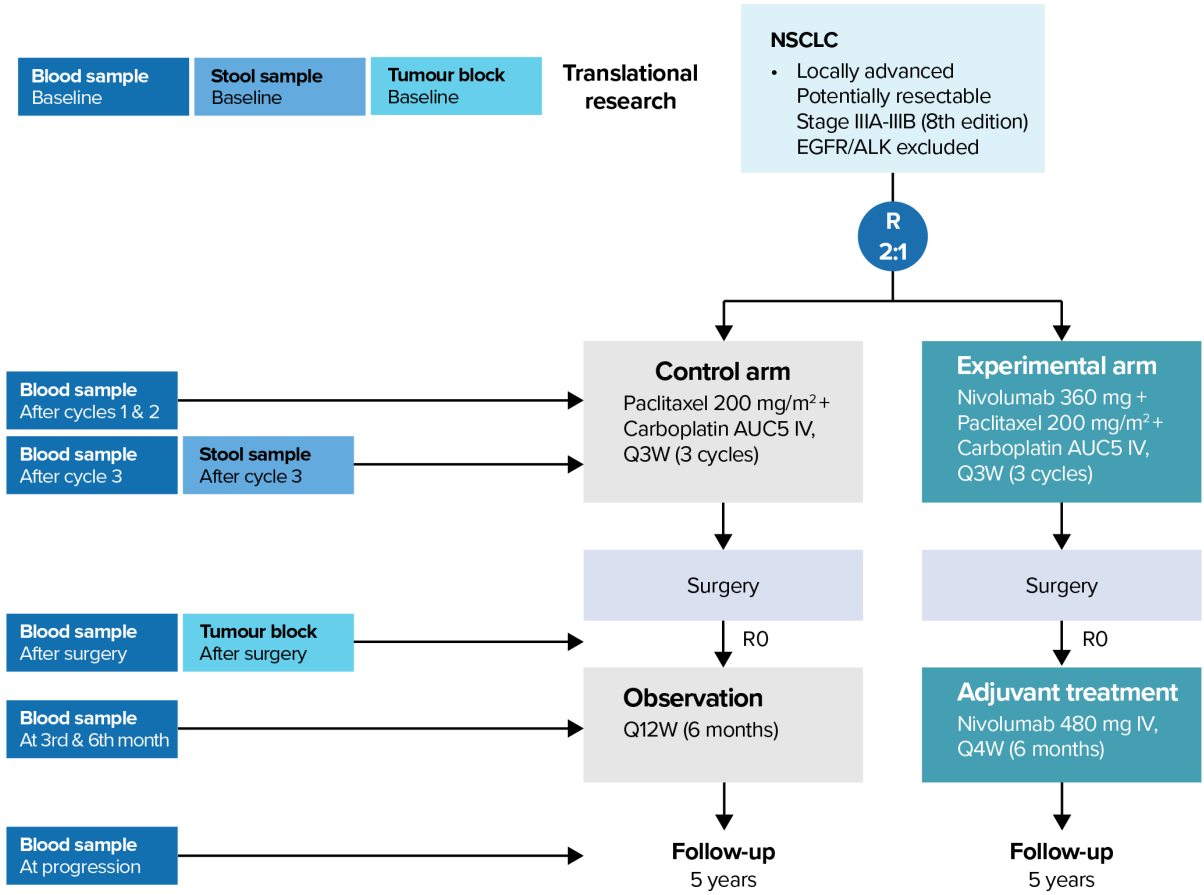
Figure 6. NADIM-II: study design



ALK = anaplastic lymphoma kinase; AUC = area under the curve; EGFR = epidermal growth factor receptor; IV = intravenous; NSCLC = non–small cell lung cancer; QxW = every x weeks.

Source: Provencio et al. (2023)[36]

Table 7. NADIM-II: summary of trial methodology

Location	21 sites in Spain	
Trial design	Open-label, multicentre, randomised, phase 2 trial	
Eligibility criteria for participants	Inclusion criteria: ▪ Males and females aged ≥ 18 years ▪ Histologically confirmed stage IIIA and potentially resectable locally advanced, stage IIIB (T3N2) NSCLC (AJCC 8th edition) ▪ Tumour considered resectable before study entry ▪ ECOG PS of 0-1 ▪ Measurable or evaluable disease (according to RECIST 1.1 criteria)	Key exclusion criteria: ▪ Known EGFR mutations or ALK translocations ▪ Patients with active, known or suspected autoimmune disease ▪ Patients with a condition requiring systemic treatment with corticosteroids or immunosuppressive medications within 14 days of randomisation ▪ Patients with a history of ILD if they have symptomatic ILD (grade 3-4) and/or poor lung function ▪ Patients with an active, known or suspected autoimmune disease

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	▪ Patients with previous malignancies unless a complete remission ≥ 2 years prior to first treatment and no additional therapy required ▪ Patients who have had prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2 or anti–CTLA-4 antibody
Settings and locations where the data were collected	See location
Trial drugs **Permitted and disallowed concomitant medication**	**Neo-Adjuvant Immunotherapy (n = 57)** ▪ Neoadjuvant treatment (200 mg/m^3 paclitaxel + AUC5 carboplatin+ 360 mg Nivolumab) started within 1-3 days from randomisation. Three cycles administered at 21-day (± 3 days) intervals (Q3W) prior to surgery. ▪ Surgery: Surgery within the 3rd-4th week (+7 days) from day 21 cycle 3 of neoadjuvant treatment (day 42-49 after day 1 of cycle 3). ▪ Adjuvant treatment: Nivolumab: 480 mg Q4W (± 3 days) for 6 months (6 cycles). Patients that are R0 confirmed by surgical pathology evaluation received the first adjuvant administration within the 3rd to 8th week (+ 7 days) from surgery and for 6 months. **Neoadjuvant chemotherapy (n = 29)** ▪ Neoadjuvant treatment (200 mg/m^3 paclitaxel + AUC5 carboplatin) started within 1-3 days from randomisation. Three cycles administered at 21-day (± 3 days) intervals (Q3W) prior to surgery. ▪ Surgery: Surgery within the 3rd-4th week (+7 days) from day 21 cycle 3 of neoadjuvant treatment (day 42-49 after day 1 of cycle 3). **Disallowed concomitant medication** ▪ Chronic use of immune suppressive drugs or corticosteroids (>10 mg daily prednisone equivalents) ▪ Any non-trial cytotoxic or immunotherapy anti-cancer treatment **Allowed concomitant medication** ▪ Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). ▪ Physiologic replacement doses of systemic corticosteroids ▪ A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions with study treatment will be delayed until corticosteroids dose ≤10 mg/day. ● G-CSF allowed as per local standard
Primary outcomes (including scoring methods and timings of assessments)	pCR: defined as the absence of residual tumour in lung and lymph nodes after neoadjuvant therapy and surgery in patients treated with chemo-immunotherapy versus patients treated with chemotherapy alone
Preplanned subgroups	Not reported

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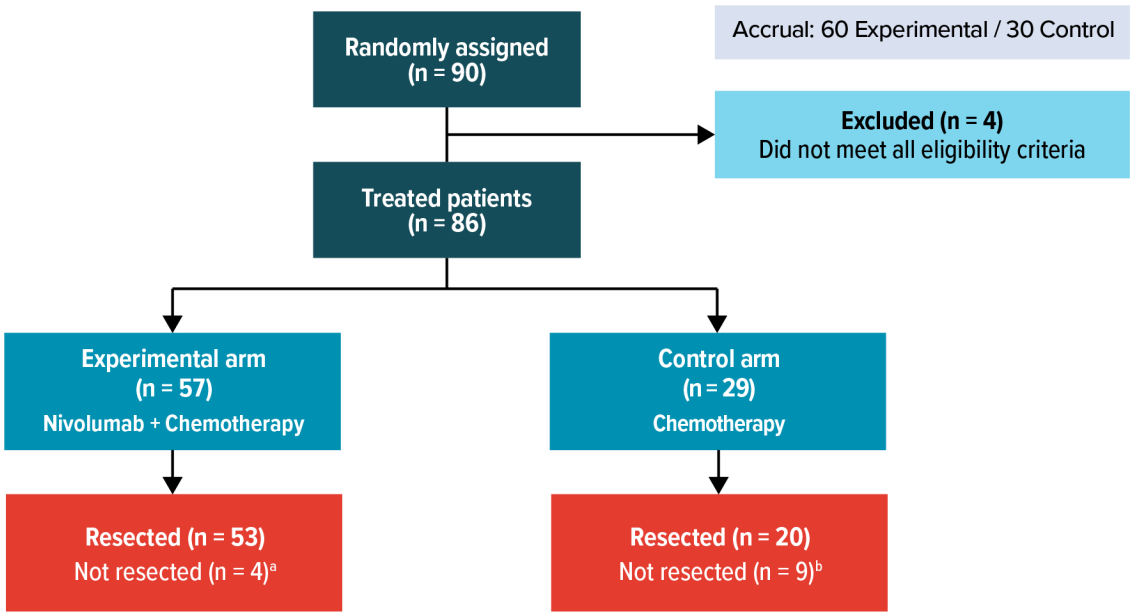
AJCC = American Joint Committee on Cancer; ALK = anaplastic lymphoma kinase; AUC = area under the curve; BICR = blinded independent central review; CTLA = cytotoxic T-lymphocyte associated protein; ECOG PS = Eastern Cooperative Oncology Group performance status; EFS = event-free survival; EGFR = epidermal growth factor receptor; ILD = interstitial lung disease IV = intravenous; pCR = pathological complete response; PD-L1 = programmed cell death-ligand 1; PD-L2 = programmed cell death-ligand 2; QxW = every x weeks; RECIST = Response Evaluation Criteria in Solid Tumours; SOC = standard of care.

Source: Provencio et al. (2023)[36]

B.3.3.2.1 NADIM-II: patient disposition and baseline characteristics

In total, 90 patients were enrolled in NADIM-II; 4 patients did not meet the inclusion criteria and were excluded. Therefore, 86 patients were randomly assigned, 57 to the nivolumab group and 29 to the control group. A total of 81 of patients (94%) completed the planned neoadjuvant treatment according to the protocol (Figure 7).

Figure 7. NADIM-II: CONSORT patient flow diagram



[a] 4 patients did not undergo surgery due to the following reasons: 1 toxicity; 1 patient's decision; 1 principal investigator's decision; 1 poor lung function.

[b] 9 patients did not undergo surgery due to the following reasons: 4 disease progression; 2 principal investigator's decision; 2 poor lung function; 1 unrelated adverse event.

Source: Provencio et al. (2023)[36]

Demographic and baseline characteristics of all randomly assigned patients in the 2 treatment arms were well balanced and were largely representative of those observed in the overall NSCLC population (Table 8).

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Table 8. NADIM-II: demographic and clinical characteristics of the patients at baseline (ITT population)[a]

Characteristic	Nivolumab + chemotherapy (N = 57)	Chemotherapy (N = 29)
Age (years), median (IQR)	65 (58-70)	63 (57-66)
Male, n (%)	36 (63)	16 (55)
ECOG PS[a]		
0	31 (54)	16 (55)
1	26 (46)	13 (45)
Node stage, n (%)		
N0	6 (11)	9 (31)
N1	10 (18)	4 (14)
N2	41 (72)	16 (55)
N2, multiple stations	22 (39)	11 (38)
Smoking status, %		
Never smoker	5 (9)	0
Former smoker	22 (39)	8 (28)
Current smoker	30 (53)	21 (72)
Histology, n (%)		
Adenocarcinoma	25 (44)	11 (38)
Adenosquamous carcinoma	1 (2)	0
Squamous cell carcinoma	21 (37)	14 (48)
Large-cell carcinoma	2 (4)	1 (3)
Not otherwise specified or undifferentiated	7 (12)	2 (7)
Other	1 (2)	1 (3)
Median tumour size (range), mm	50 (15-155)	52 (15-166)
TNM classification, no (%)[b]		
T1N2M0	12 (21)	4 (14)
T2N2M0	16 (28)	7 (24)
T3N1M0	2 (4)	1 (3)
T3N2M0	13 (23)	5 (17)
T4N0M0	6 (11)	9 (31)
T4N1M0	8 (14)	3 (10)

AJCC = American Joint Committee on Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; ITT = intention to treat; TNM = tumour-node-metastasis.

Note: The ITT population included all the patients who had undergone randomisation and received at least 1 cycle of neoadjuvant treatment. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

[a] ECOG PS scores range from 0 to 5, with higher scores indicating greater disability.

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[b] TNM staging was based on the 8th edition of the AJCC Cancer Staging Manual. The reasons for T4 designation were a tumour size of greater than 7 cm (14 patients), invasion of great vessels (5 patients), mediastinal invasion (2 patients), separate tumour nodule in the same lobe of the primary tumour (2 patients), invasion of the chest wall (1 patient), invasion of the diaphragm (1 patient), and invasion of vertebral bodies (1 patient). The reasons for T3 designation were a tumour size of greater than 5 cm but less than 7 cm (14 patients), separate tumour nodule in the same lobe of the primary tumour (5 patients), and invasion of the parietal pleura (2 patients). Among the patients with T3N1M0 classification, the reasons for T3 designation were a tumour size of greater than 5 cm but less than 7 cm (2 patients) and separate tumour nodule in the same lobe of the primary tumour (1 patient). N2 status was further confirmed by means of endobronchial ultrasound–guided bronchoscopy (31 patients), mediastinoscopy (4 patients), or transthoracic fine-needle aspiration (22 patients). The average number of stations sampled was 1.95 (range, 1-5).

Source: Provencio et al. (2023)[36]

B.3.4 Critical appraisal of the relevant clinical effectiveness evidence

Table 9 presents the quality assessment for CheckMate-77T and NADIM-II. CheckMate-77T was a phase III, double-blind, randomised, placebo-controlled trial. The use of placebo as a control allowed for a more objective evaluation of the efficacy and safety of nivolumab, and the study design was considered ethically justified considering participants would either receive the SOC at the time, or an immunotherapy, which could potentially demonstrate clinical benefit in this perioperative setting.[6]

Patients meeting eligibility criteria were randomly assigned to 1 of the treatment arms through interactive response technology (IRT). Treatment allocation (nivolumab vs. placebo) was only available through the IRT to an unblinded pharmacist or other individual(s) who was responsible for the dispensing of blinded study drug but not involved in any other aspect of the study. Demographics and baseline disease characteristics were balanced between treatment arms (see Section B.3.3.1.1) and generally representative of the population with resectable NSCLC. A blinded independent pathology review (BIPR) was used to review pathological data and tumour assessment for all randomly assigned patients.

Although neoadjuvant chemotherapy was the comparator used in CheckMate-77T, the current SOC in England is now perioperative pembrolizumab; however, this treatment was recommended after the CheckMate-77T trial was conducted.

Detailed methods are not reported in Provencio et al. (2023)[36] for NADIM-II, therefore some aspects of the quality assessment are unclear. Although this is an open-label study conducted in 21 centres in Spain, having 2 studies comparing perioperative nivolumab versus neoadjuvant chemotherapy helps mitigate any uncertainty in the treatment effect and clinical benefit of perioperative nivolumab.

NADIM-II included patients with stage IIIA or IIIB NSCLC – which differed to that of CheckMate-77T (which include patients with resectable stage IIA to IIIB NSCLC).[4,6] The treatment regimen in the NADIM-II experimental arm was nivolumab 360 mg + chemotherapy every 3 weeks for 3 cycles, followed by surgery and then nivolumab 480 mg every 4 weeks for up to 6 months. Again, this differs from the CheckMate-77T (nivolumab 360 mg + chemotherapy every 3 weeks for 4 cycles, followed by surgery and then nivolumab 480 mg every 4 weeks for up to approximately 1 year). Having a study that better reflects

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clinical practice in Europe (while CheckMate-77T is a global study that include very heterogeneous countries/centres) is useful to complement the evidence base for perioperative nivolumab.

Table 9. Quality assessment

Criteria	CheckMate-77T	NADIM-II
Was randomisation carried out appropriately?	Yes	Not clear
Was concealment of treatment allocation adequate?	Yes	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	No
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	No (open label)
Were there any unexpected imbalances in dropouts between groups?	No	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis?	Yes	Yes
If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
How closely does the RCT(s) reflect routine clinical practice?	Unclear—current SOC in England is perioperative pembrolizumab rather than neoadjuvant chemotherapy.	Study was conducted in Spain. Regimen used for nivolumab is not the label regimen and the included population was of more limited stage than in the label.

RCT = randomised controlled trial; SLR = systematic literature review; SOC = standard of care.

Sources: BMS data on file (2023)[37]; Provencio et al. (2023)[36]

B.3.5 Clinical effectiveness results

B.3.5.1 CheckMate-77T

At the time of the 16 December 2024 database lock, the median follow-up was [redacted][5]

The descriptive analysis supports the statistically significant improvement seen in the first interim analysis (September 2023), demonstrating a meaningful improvement in EFS per

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blinded independent central review (BICR) with perioperative nivolumab versus neoadjuvant chemotherapy in patients with resectable stage IIA-IIIB NSCLC (see Section B.3.5.1.1). Results for EFS per BICR favoured the nivolumab group over the chemotherapy group across most subgroups of tumour programmed cell death-ligand 1 (PD-L1) (< 1%, ≥ 1%, 1%-49%, ≥ 50%), histology (non-squamous, squamous), and disease stage (II, III).

The results for the primary endpoint (EFS per BICR) were supported by clinically meaningful improvements in the nivolumab group compared with the chemotherapy group for secondary (pCR and MPR per BIPR) and exploratory endpoints (objective response rate [ORR] per BICR, time to death or distant metastases [TTDM] per investigator, and EFS after next line of treatment [EFS2] per investigator); further detail is presented in Sections B.3.5.1.1 to B.3.5.1.6.

B.3.5.1.1 EFS per BICR (primary endpoint)

Event-free survival was defined as the time from randomisation to any event of progression of disease or worsening of disease precluding surgery, if 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.

As of the 16 December 2024 database lock, median EFS, the primary outcome, was [redacted] (95% confidence interval [CI], [redacted]) in the nivolumab group, and [redacted] (95% CI, [redacted]) in the chemotherapy group (HR for disease progression or recurrence, abandoned surgery, or death, [redacted] [95% CI, [redacted]]) (Table 10, Figure 8).

Table 10. CheckMate-77T: event-free survival per BICR (primary endpoint): all randomly assigned patients (ITT population)

	Nivolumab (N = 229)	Chemotherapy (N = 232)
Events, n (%)	[redacted]	[redacted]
Median EFS (95% CI, months)[a]	[redacted]	[redacted]
HR (95% CI)	[redacted]	
24 months, %	[redacted]	[redacted]
30 months, %	[redacted]	[redacted]

BICR = blinded independent central review; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; ITT = intention to treat; NR = not reached.

[a] Based on Kaplan-Meier estimates.

Source: BMS data on file (2025)[5]

Figure 8. CheckMate-77T: event-free survival per BICR, primary definition: all randomly assigned patients (ITT population)

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BICR = blinded independent central review; Chemo = chemotherapy; CI = confidence interval; EFS = event-free survival; ITT = intention to treat; NIVO = nivolumab; NR = not reached; PBO or Pla = placebo.

Source: BMS data on file (2025)[5]

B.3.5.1.2 Overall survival (secondary endpoint)

OS was defined as the time between the date of randomisation and the date of death due to any cause. OS was censored on the last date a patient was known to be alive.[37]

At the first prespecified interim analysis for OS (16 December 2024), median OS was [redacted] (HR for death, [redacted] [97.63% CI, [redacted]]) (Table 11, Figure 9). However, the study will continue as planned and OS will be tested at final analysis, which is planned at approximately 174 events.[5]

Table 11. CheckMate-77T: overall survival—all randomly assigned patients (ITT population)

	Nivolumab (N = 229)	Chemotherapy (N = 232)
Events, n (%)	[redacted]	[redacted]
Median OS (95% CI, months)	[redacted]	[redacted]
HR (97.63% CI)	[redacted]	
HR (95% CI)	[redacted]	
P value	[redacted]	
24 months, %	[redacted]	[redacted]

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	Nivolumab (N = 229)	Chemotherapy (N = 232)
30 months, %	[redacted]	[redacted]

CI = confidence interval; EFS = event-free survival; HR = hazard ratio; ITT = intention to treat; NR = not reached.

Source: BMS data on file (2025)[5]

Figure 9. CheckMate-77T: overall survival—all randomly assigned patients (ITT population)

Chemo = chemotherapy; CI = confidence interval; EFS = event-free survival; ITT = intention to treat; NIVO = nivolumab; NR = not reached; PBO or Pla = placebo.

Source: BMS data on file (2025)[5]

B.3.5.1.3 Pathologic response per BIPR (pCR rate and MPR rate, secondary endpoints)

Pathologic complete response (pCR) by BIPR was defined as the number of randomly assigned patients with absence of residual viable tumour in lung and lymph nodes as evaluated by BIPR, divided by the number of randomly assigned participants for each arm.

At the database lock of 6 September 2023 (median follow-up, 25.4 months [range, 15.7-44.2 months]), compared with the chemotherapy group, pCR was higher among patients in the nivolumab group (Table 12, Figure 10). A pCR occurred in 25.3% of the patients in the nivolumab group (95% CI, 19.8%-31.5%) and in 4.7% of those in the chemotherapy group (95% CI, 2.4%-8.3%).

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Major pathological response was defined as the number of randomly assigned patients with ≤ 10% residual viable tumour in lung and lymph nodes as evaluated by BIPR, divided by the number of randomly assigned participants for each arm. An MPR by BIPR also occurred in more patients in the nivolumab group (35.4%; 95% CI, 29.2%-41.9%) than in the chemotherapy group (12.1%; 95% CI, 8.2%-17.0%) (Table 12, Figure 10).[6]

A sensitivity analysis of pCR per BIPR in all response-evaluable patients was consistent with the primary analysis and favoured the nivolumab group (pCR: 37.2% vs. 6.9%; MPR: 51.9% vs. 17.6%).[37]

Table 12. CheckMate-77T: pathological complete response (per BIPR) and major pathological response (per BIPR)–all randomly assigned patients (ITT population)

	Nivolumab (N = 229)	Chemotherapy (N = 232)
Pathologic complete response[a] per BIPR		
Responders, n (%)	58 (25.3)	11 (4.7)
95% CI[b]	19.8-31.5	2.4-8.3
Difference (95% CI)[c,d]	20.5 (14.3-26.6)	
Estimate of odds ratio (95% CI)[d,e]	6.64 (3.40-12.97)	
Major pathologic response[a] per BIPR		
Responders, n (%)	81 (35.4)	28 (12.1)
95% CI[b]	29.2-41.9	8.2-17.0
Difference (95% CI), %[c,d]	23.2 (15.8-30.6)	
Estimate of odds ratio (95% CI)[d,e]	4.01 (2.48-6.49)	

BIPR = blinded independent pathology review; CI = confidence interval; IRT = interactive response technology; ITT = intention to treat; PD-L1 = programmed cell death-ligand 1.

[a] Randomly assigned patients who were no longer eligible for surgery, or who were on alternative anticancer therapy before surgery, or who discontinued the study before surgery were all counted as non-responders. In both arms, < 5% of randomly assigned patients did not provide tumour samples after surgery.

[b] Confidence interval based on the Clopper and Pearson method.

[c] Strata-adjusted difference based on Cochran–Mantel–Haenszel method of weighting.

[d] Stratified by randomisation stratification factors (tumour PD-L1 status [≥ 1% vs. < 1%/not evaluable/ indeterminate], disease stage [II vs. III], histology [squamous vs. non-squamous] per IRT).

[e] Strata-adjusted odds ratio using Mantel–Haenszel method.

Sources: BMS data on file (2023)[37]; Cascone et al. (2024)[6]

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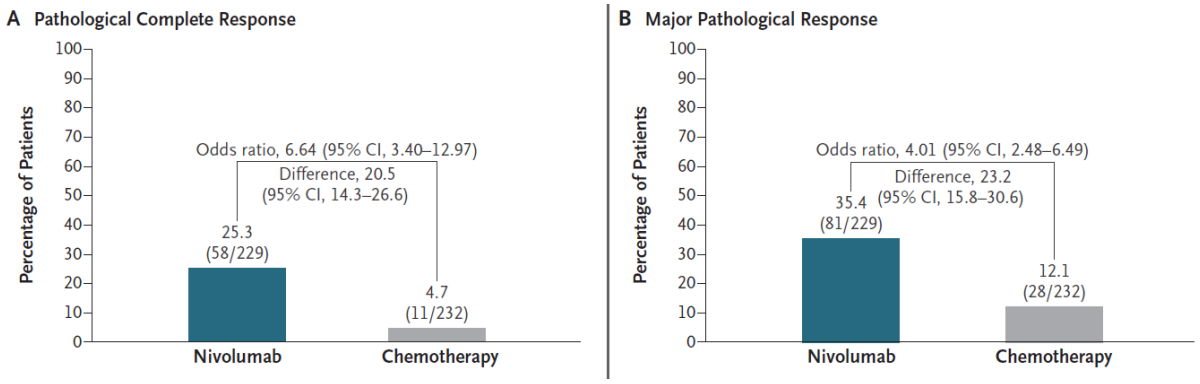
Figure 10. CheckMate-77T: pathological complete response and major pathological response



CI = confidence interval.

Source: Cascone et al. (2024)[6]

B.3.5.1.4 Objective response rate per BICR (exploratory endpoint)

At the 6 September 2023 database lock (median follow-up, 25.4 months [15.7-44.2]), an improvement in BICR-assessed ORR was observed with nivolumab versus chemotherapy (Table 13).[6] Investigator-assessed ORR for the nivolumab and chemotherapy groups were comparable with those per BICR: 61.1% (95% CI, 54.5-67.5) vs. 42.7% (95% CI, 36.2-49.3).[37]

Table 13. CheckMate-77T: objective response rate and best overall response: all randomly assigned patients (ITT population)

Response	Nivolumab + chemotherapy/nivolumab (N = 229)	Placebo + chemotherapy/placebo (N = 232)
Objective response rate, n (%)[a]	133 (58.1)	99 (42.7)
95% CI	(51.4-64.5)	(36.2-49.3)
Odds ratio (95% CI)	1.90 (1.30-2.76)	
Best overall response, n (%)		
Complete response	7 (3.1)	6 (2.6)
Partial response	126 (55.0)	93 (40.1)
Stable disease	73 (31.9)	107 (46.1)
Progressive disease	9 (3.9)	13 (5.6)
Unable to be determined	14 (6.1)	13 (5.6)

CI = confidence interval; ITT = intention to treat.

Confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing.

[a] Objective response was defined as complete response or partial response according to Response Evaluation Criteria in Solid Tumours, version 1.1, before definitive surgery without confirmation.

Source: Cascone et al. (2024)[6]

B.3.5.1.5 Time to death or distant metastases per investigator (exploratory endpoint)

At the 6 September 2023 database lock (median follow-up, 25.4 months [range, 15.7-44.2 months]), median TTDM per investigator was not reached in the nivolumab arm and

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38.77 months (95% CI, 21.19 months to not applicable) in the placebo arm (Table 14, Figure 11).[37] The TTDM rates (95% CI) at 15 months were numerically higher in the nivolumab arm compared with the chemotherapy arm: 77.1% (95% CI, 70.7%-82.3%) versus 65.9% (95% CI, 59.0%-71.9%).

Table 14. CheckMate-77T: time to death or distant metastasis per investigator—all randomly assigned patients (ITT population)

	Nivolumab (N = 229)	Chemotherapy (N = 232)
TTDM per investigator		
Events, n (%)	61 (26.6)	91 (39.2)
Median TTDM (95% CI) months[a]	NA	38.77 (21.19-NA)
HR (95% CI)[b]	0.62 (0.44-0.85)	
TTDM rates (95% CI), %[a]		
6 months	90.4 (85.6-93.6)	89.3 (84.3-92.8)
12 months	81.3 (75.3-86.0)	71.4 (64.8-77.0)
15 months	77.1 (70.7-82.3)	65.9 (59.0-71.9)

CI = confidence interval; HR = hazard ratio; IRT = interactive response technology; ITT = intention to treat; NA = not applicable; PD-L1 = programmed cell death-ligand 1; TTDM = time to death or distant metastases.

[a] Based on Kaplan-Meier estimates.

[b] HR of arm A to arm B from a Cox proportional hazard model stratified by randomisation stratification factors: tumour PD-L1 status (≥ 1% vs. < 1%/not evaluable/indeterminate), disease stage (II vs. III), and histology (squamous vs. non-squamous) per IRT.

Sources: BMS data on file (2023)[37]; Cascone et al. (2024)[6]

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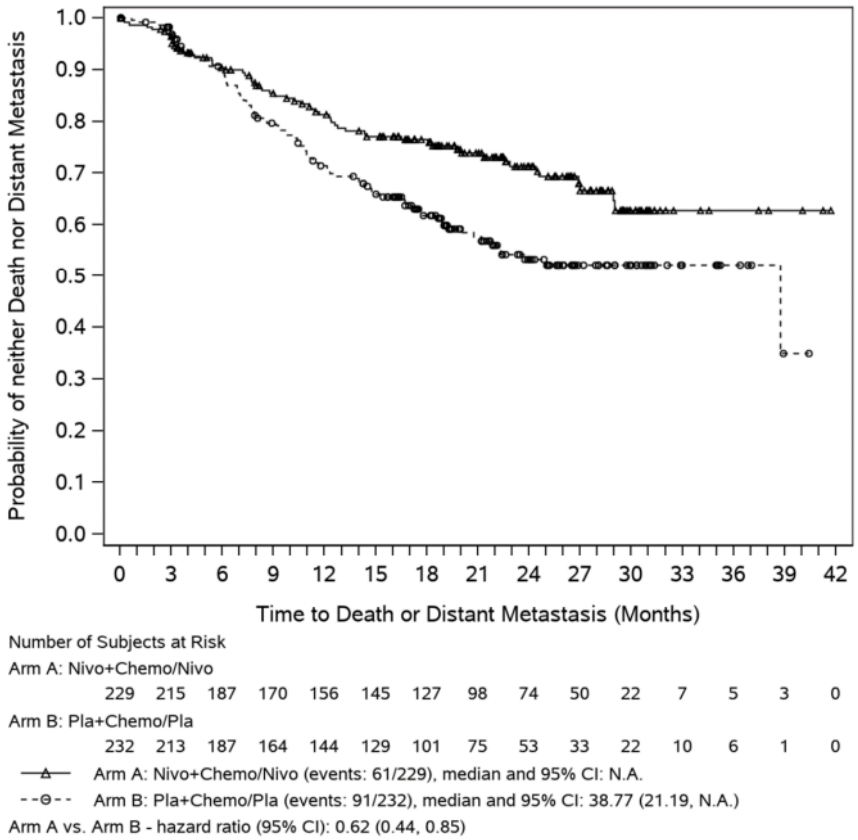
Figure 11. CheckMate-77T: time to death or distant metastasis per investigator—all randomly assigned patients (ITT population)



Chemo = chemotherapy; CI = confidence interval; ITT = intention to treat; N.A. = not applicable; Nivo = nivolumab; Pla = placebo.

Notes: Symbols represent censored observations.

Statistical model for hazard ratio: stratified Cox proportional hazard model.

Source: BMS data on file (2023)[37]

B.3.5.1.6 Event-free survival on next line of therapy per investigator (exploratory endpoint)

At the 6 September 2023 database lock (median follow-up, 25.4 months [range, 15.7-44.2 months]), the HR for EFS2 per investigator favoured the nivolumab group over the chemotherapy group (Table 15, Figure 12). Patients who were alive and without progression on the next line of therapy were censored at the last known alive date.

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Table 15. CheckMate-77T: event-free survival 2 per investigator—all randomly assigned patients (ITT population)

	Nivolumab (N = 229)	Chemotherapy (N = 232)
EFS2 per investigator		
Events, n (%)	47 (20.5)	56 (24.1)
Median EFS2 (95% CI), months[a]	NR (38.57-NA)	NR (NA-NA)
HR (95% CI)[b]	0.83 (0.56-1.23)	

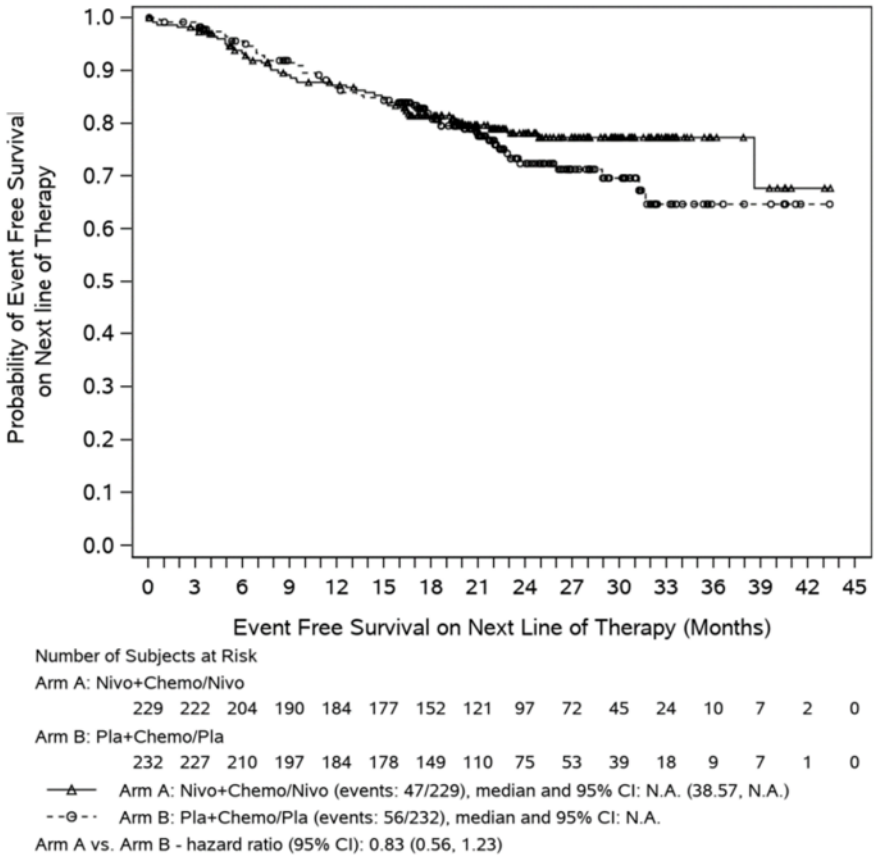
CI = confidence interval; EFS2 = event-free survival after next line of treatment; HR = hazard ratio; IRT = interactive response technology; ITT = intention to treat; NA = not applicable; NR = not reached; PD-L1 = programmed cell death-ligand 1.

[a] Based on Kaplan-Meier estimates.

[b] HR of arm A to arm B from a Cox proportional hazard model stratified by randomisation stratification factors: tumour PD-L1 status (≥ 1% vs. < 1%/not evaluable/indeterminate), disease stage (II vs. III), and histology (squamous vs. non-squamous) per IRT.

Source: BMS data on file (2023)[37]

Figure 12. CheckMate-77T: event-free survival on next line of therapy (EFS2)—all randomly assigned participants in the global population



Chemo = chemotherapy; CI = confidence interval; EFS2 = event-free survival after next line of treatment; N.A. = not applicable; Nivo = nivolumab; Pla = placebo.

Note: Statistical model for hazard ratio: Stratified Cox proportional hazard model. Symbols represent censored observations.

Source: BMS data on file (2023)[37]

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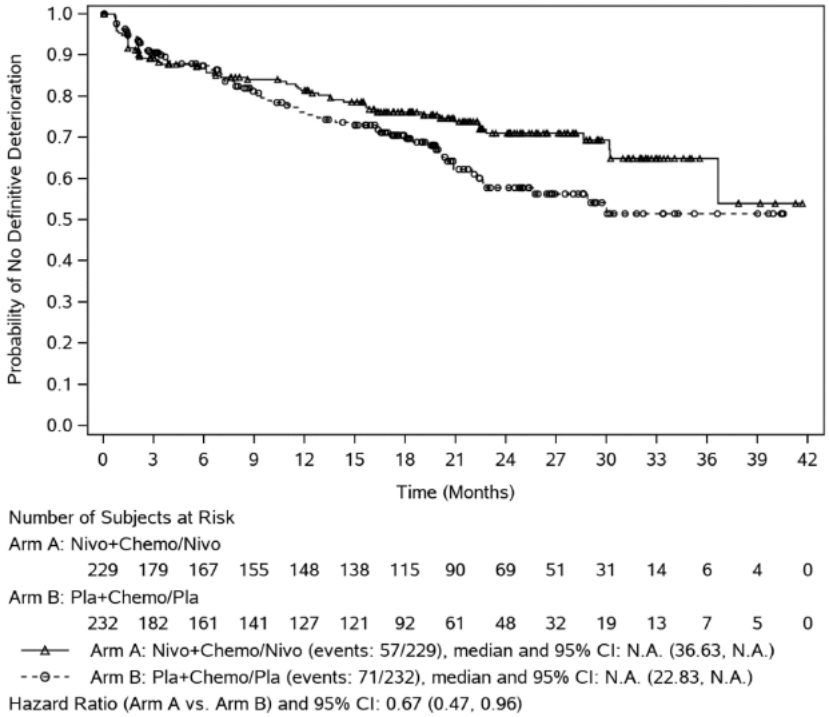
B.3.5.1.7 Health-related quality of life

At the 6 September 2023 database lock (median follow-up, 25.4 months [range, 15.7-44.2 months]), mean baseline EQ-5D-3L visual analogue scale (VAS) and utility index scores reported were similar in the nivolumab and chemotherapy groups. After controlling for baseline score and relevant covariates, patients in the nivolumab and chemotherapy arms had small improvements (increase) in EQ-5D-3L VAS scores overall (during the neoadjuvant, surgical, and adjuvant periods). The change from baseline least squares mean (95% CI) was 1.07 (−0.46 to 2.61) versus 1.67 (0.14-3.19). Thus, HRQOL appeared to be maintained when using nivolumab.

The median time to definitive deterioration in EQ-5D-3L VAS score was not reached in either arm. Participants in the nivolumab arm had a decreased risk of definitive deterioration (HR, 0.67; 95% CI, 0.47-0.96) compared with patients in the placebo arm (Figure 13).

Figure 13. CheckMate-77T: time to definitive deterioration in EQ-5D-3L visual analogue score (overall self-rated health status)—all randomly assigned patients



Chemo = chemotherapy; CI = confidence interval; N.A. = not applicable; Nivo = nivolumab; Pla = placebo.

Notes: Symbols represent censored observations.

Stratified Cox proportional hazard model with baseline patient-reported outcome score as a covariate.

The baseline is defined as last assessments performed prior to neoadjuvant C1D1 treatment.

Definitive deterioration is defined as a change from baseline of 7 with no further improvement in score or any further data.

Source: BMS data on file (2023)[37]

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B.3.5.2 NADIM-II

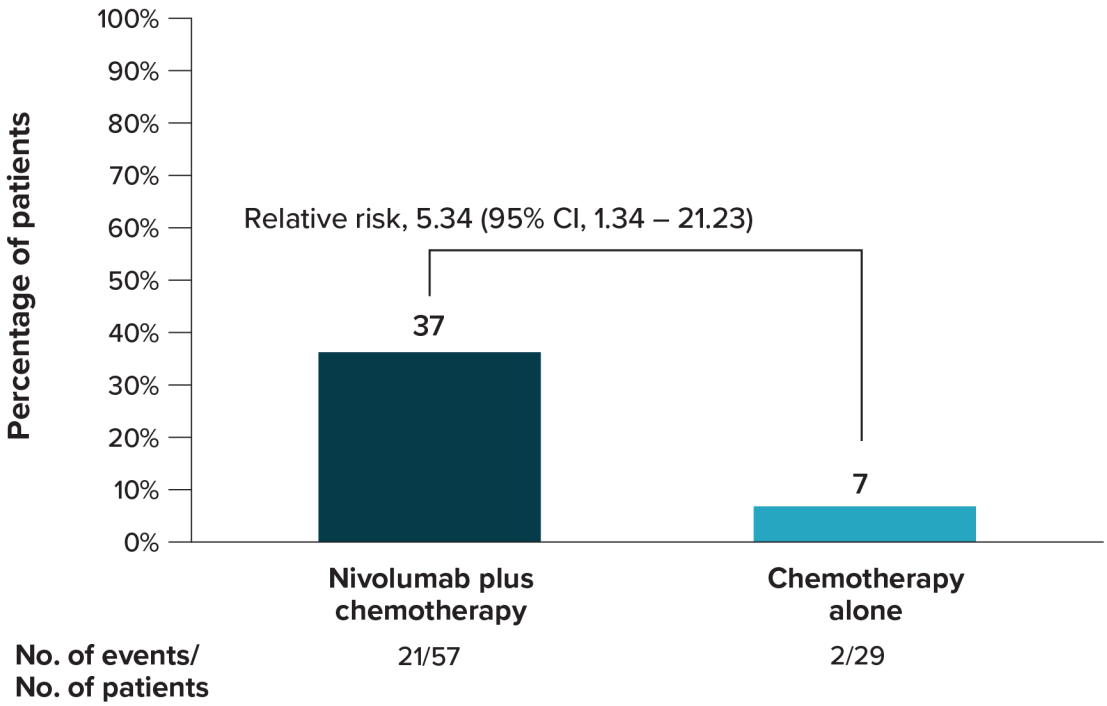
At the time of the analysis, median follow-up was 26.1 months (interquartile range, 17.4-30.9 months), with 95.2% data maturity at 24 months. The results for the primary endpoint (pCR after neoadjuvant therapy and surgery) were supported by clinically meaningful improvements in the nivolumab group compared with the chemotherapy group for secondary endpoints (progression-free survival [PFS] and OS at 24 months).[36]

B.3.5.2.1 Pathological complete response (primary endpoint)

Pathological complete response (pCR) was defined as a complete absence of viable tumour cells in the primary tumour site and surgically removed lymph nodes after neoadjuvant treatment and surgery, as determined by BICR. Patients with tumours that were not surgically resectable after neoadjuvant treatment were considered to have not had a response.[36]

The addition of nivolumab to neoadjuvant chemotherapy resulted in a significantly higher percentage of patients with a pCR than chemotherapy alone. In the intention-to-treat (ITT) population, a pCR occurred in 37% of patients in the nivolumab group (95% CI, 24%-51%), and in 7% of patients in the chemotherapy group (95% CI, 1%-23%; relative risk, 5.34; 95% CI, 1.34-21.23; *P* = 0.02) (Figure 14).

Figure 14. NADIM-II: pathological complete response per BICR (ITT population)



BICR = blinded independent central review; CI = confidence interval; ITT = intention to treat.

Source: Provencio et al. (2023)[36]

B.3.5.2.2 Progression-free survival (secondary endpoint)

Progression-free survival was defined as the time from randomisation to progression of disease, recurrence of disease, or death from any cause at 24 months. At 24 months, PFS

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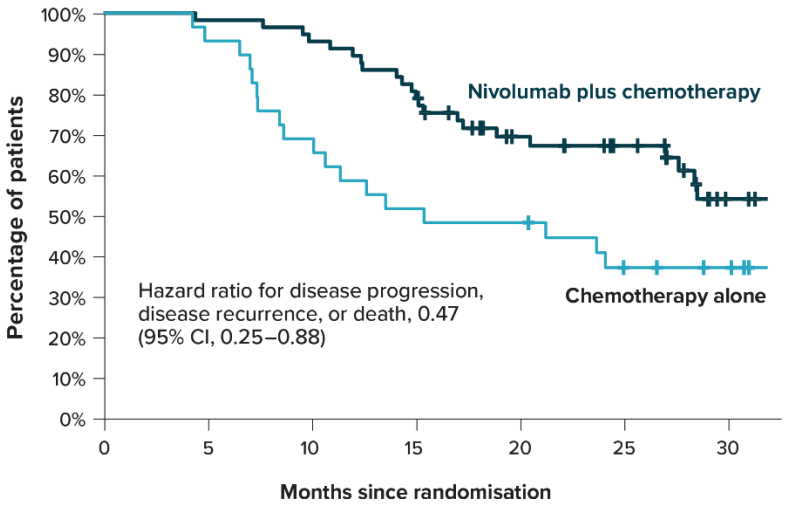
was 67.2% (95% CI, 55.8%-81.0%) in the nivolumab group and 40.9% (95% CI, 26.2%-63.6%) in the chemotherapy group. The median PFS was not reached (95% CI, 27.6 months to not reached) in the nivolumab + chemotherapy group and was 15.4 months (95% CI, 10.6 months to not reached) in the chemotherapy-alone group (HR, 0.47; 95% CI, 0.25-0.88) (Figure 15).

Figure 15. NADIM-II: progression-free survival per BICR (ITT population)



No. at Risk							
Nivolumab plus chemotherapy	57	56	53	45	31	25	11
Chemotherapy alone	29	27	20	15	14	9	7

BICR = blinded independent central review; CI = confidence interval; ITT = intention to treat.

Source: Provencio et al. (2023)[36]

B.3.5.2.3 Overall survival (secondary endpoint)

Overall survival was defined as the time from randomisation to death from any cause. Overall survival at 24 months was 85.0% (95% CI, 75.9%-95.2%) in the nivolumab group and 63.6% (95% CI, 47.8%-84.6%) in the chemotherapy group. Median OS had not been reached in either group (hazard ratio [HR] for death, 0.43; 95% CI, 0.19-0.98) (Figure 16).

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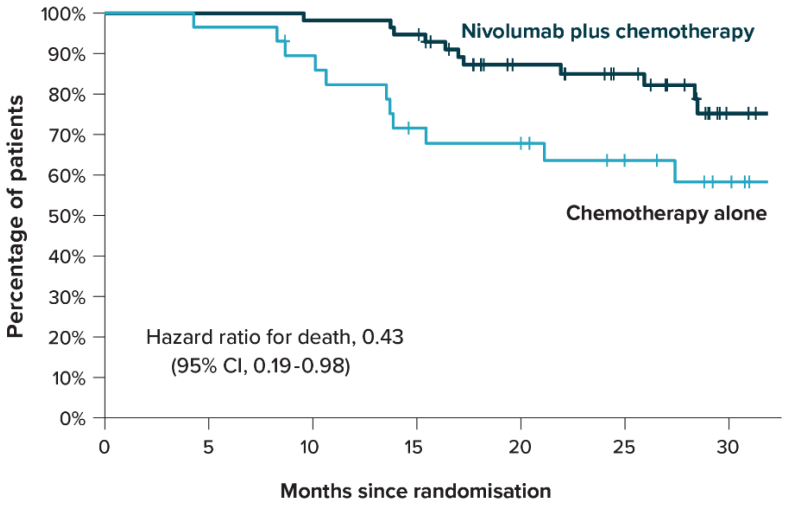
Figure 16. NADIM-II: Kaplan-Meier curve for overall survival (ITT population)



No. at Risk							
Nivolumab plus chemotherapy	57	57	56	54	38	32	15
Chemotherapy alone	29	28	25	19	17	13	9

BICR = blinded independent central review; CI = confidence interval; ITT = intention to treat.

Source: Provencio et al. (2023)[36]

B.3.6 Subgroup analysis

BMS intend to seek reimbursement for the ITT population of the CheckMate-77T trial, in line with the MHRA licence[4] and the NICE reimbursement of perioperative pembrolizumab, and therefore do not intend to explore subgroups for this appraisal.

B.3.7 Meta-analysis

No head-to-head evidence comparing perioperative nivolumab and perioperative pembrolizumab was available; therefore, an ITC was required to assess the clinical similarity of the treatments.

B.3.8 Indirect and mixed treatment comparisons

The ITC conducted was performed as part of an extensive global project for assessing treatment efficacy across multiple treatments of patients with stage II-IIIB resectable non-metastatic NSCLC. As pembrolizumab is the only comparator of interest for the current analysis, only summary results and methods pertaining to that comparison are presented here. Description of the full ITC and details of the data and methods used can be found in Appendix D. A summary of the approaches used and results relevant to the comparison with pembrolizumab is presented in this section.

The methodological framework for the ITC included different methods of quantitative evidence synthesis that addressed different aspects of the evidence base. The first approach involved traditional Bayesian network meta-analysis (NMA); the second approach consisted of a fractional polynomial (FP)–NMA, which relaxed the proportional hazards (PH)

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assumption required by traditional Bayesian NMA; the third approach, a multilevel network meta-regression (ML-NMR) was explored to generate estimates of relative effect adjusted to the population in CheckMate-77T.

Quantitative evidence synthesis relied on data extracted from the SLR of RCTs, updated in November 2024 (see Section B.3.1). The primary outcomes of interest were EFS and OS. Table 16 presents the trials used to carry out the ITC, and Section B.3 and Appendix A present detail of the trials.

Table 16. Summary of the trials used to carry out the indirect treatment comparison

Reference of trial	Perioperative nivolumab + neoadjuvant chemotherapy	Perioperative pembrolizumab + neoadjuvant chemotherapy
Trial 1	CheckMate-77T	KEYNOTE-671
Trial 2	NADIM-II	

B.3.8.1 Traditional Bayesian network meta-analysis

In the traditional, proportional hazards Bayesian NMA, the ITC result for EFS showed that the comparison between perioperative nivolumab and perioperative pembrolizumab was associated with an HR that was very close to 1 (HR [95% credible interval (CrI)], [redacted]) with wide uncertainty in the CrI, indicating strong similarity in EFS between these 2 regimens.

Similarly, the comparison between perioperative nivolumab and perioperative pembrolizumab demonstrated strong similarity in OS, with CrIs that were close to the null value of 1 ([redacted]). These results demonstrate sufficient similarity between perioperative nivolumab and perioperative pembrolizumab.

B.3.8.2 Fractional polynomial network meta-analysis

The traditional Bayesian NMA requires the PH assumption—which assumes a constant HR over time—to be met. Based on statistical tests of the PH assumption, the PH assumption was rejected in one of the RCTs comparing immuno-oncology–based and non–immuno-oncology regimens ([redacted]), and a possible trend was observed in a second immuno-oncology–based versus non–immuno-oncology RCT ([redacted]). However, the PH assumption was not rejected in CheckMate-77T, nor did visual inspections suggest obvious deviations. Although, with longer follow-up, it remains possible that such trends may emerge. Thus, there was uncertainty regarding the use of a PH model.

To address this, an FP-NMA was conducted, which allows for non-linear modelling of treatment effects over time (time-varying HRs).

In the FP-NMA, with respect to EFS, the best-ranked model in terms of deviance information criterion (DIC) was a time-constant HR Weibull model. However, for the base-case analysis applying the predefined heuristic process (which included 3 other components: reasonable model complexity, good alignment with the modelled vs. observed survival curves based on

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visual inspection, and clinically plausible projections beyond the observed period), the final selected model was a second-order Weibull-based FP, having powers of [redacted] and [redacted], and where treatment effects were placed on the [redacted]. This was the best-ranked time-varying HR model based on DIC and the second-best model overall based on DIC. The results from this model for the comparison between perioperative nivolumab and perioperative pembrolizumab were consistent with the standard NMA results, showing HRs close to 1 irrespective of time (HR, [redacted]; 95% CrI, [redacted]). Table 17 presents the numerical EFS HR estimates of perioperative nivolumab versus perioperative pembrolizumab over 60 months.

Table 17. Event-free survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the fractional polynomial network meta-analysis

Time	HR (95% CrI)
3	[redacted]
6	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]
30	[redacted]
36	[redacted]
42	[redacted]
48	[redacted]
54	[redacted]
60	[redacted]

CrI = credible interval; HR = hazard ratio.

With respect to OS, the final selected model was a second-order Weibull-based FP, having powers of [redacted] and [redacted], and where treatment effects were placed on the first and third terms. This was the best-ranked time-varying model based on DIC that best addressed all the 3 other components of the heuristic process described above for EFS. The comparison between perioperative nivolumab and perioperative pembrolizumab showed that HRs trended upwards over time and [redacted] over the first year (at 3 months: [redacted]), [redacted] at 60 months ([redacted]), with CrIs [redacted] for all evaluated timepoints, demonstrating OS similarity. Table 18 presents the numerical OS HR estimates of perioperative nivolumab versus perioperative pembrolizumab over 60 months. It is important to note that median follow-up in the CheckMate-77T and KEYNOTE-671 trials for data used in this analysis was [redacted]; the HRs at later time points should be interpreted with caution due to high censoring and limited follow-up.

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Table 18. Overall survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the fractional polynomial network meta-analysis

Time	HR (95% CrI)
3	[redacted]
6	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]
30	[redacted]
36	[redacted]
42	[redacted]
48	[redacted]
54	[redacted]
60	[redacted]

CrI = credible interval; HR = hazard ratio.

B.3.8.3 Multilevel network meta-regression

Alongside the previously described traditional Bayesian NMA and FP-NMA that were conducted, an ML-NMR was also conducted. An ML-NMR is a population-level adjustment method that represents an extension of the standard network NMA framework and can be applied to a network of evidence aimed to reduce bias by adjusting for imbalances in patient populations across trials.[40]

A key assumption of traditional NMA is that effect modifiers are evenly distributed across trials; when this assumption is violated, ITCs may yield biased estimates. Given the misalignment in treatment effect modifiers between the CheckMate-77T and KEYNOTE-671 trials, i.e., the proportion of patients having stage III disease at baseline and the proportion of patients with PD-L1 expression levels ≥ 1% in the KEYNOTE-671 were higher than in CheckMate-77T, the use of ML-NMR helps adjust for these imbalances in patient characteristics across studies. Additionally, whereas a main benefit of the FP-NMA is the ability to model HRs that vary over time, the ML-NMR can do the same, while also making population-based adjustments that address imbalances in patient characteristics across the network of evidence. As such, ML-NMR is considered the most methodologically robust ITC approach in this context, allowing for more reliable estimates of relative treatment effects.

Population-adjustment factors were established using clinical input during 2 different advisory board meetings, evidence collected from an SLR, and external evidence identified in advanced NSCLC populations. Disease stage was identified as a prognostic factor with strong clinical and empirical evidence, while PD-L1 expression level was identified as an effect modification factor with strong clinical and empirical evidence.

Consequently, disease stage and PD-L1 expression level were included for adjustment in the ML-NMR. The main target population for the analysis was defined by the CheckMate-

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77T trial population. Table 19 summarises the key baseline characteristics that were relevant to the ML-NMR adjustment by study.

Table 19. Key baseline characteristics across the network of evidence informing the multilevel network meta-regression by study

Trial	Regimen (n)	Stage III (%)	PD-L1 ≥ 1% (%)
CheckMate-77T	Perioperative nivolumab + neoadjuvant chemotherapy (229), neoadjuvant chemotherapy (232)	65	56[a]
NADIM-II	Perioperative nivolumab +neoadjuvant chemotherapy (57), neoadjuvant chemotherapy (29)	100	52
KEYNOTE-671	Perioperative pembrolizumab + neoadjuvant chemotherapy (397), neoadjuvant chemotherapy (400)	70	64

PD-L1 = programmed cell death-ligand 1.

[a] Patients with non-evaluable PD-L1 expression level were assumed to have PD-L1< 1%, rather than being excluded or using imputation.

After adjusting for PD-L1 ≥ 1% and stage III differences between patients in the CheckMate-77T and KEYNOTE-671 clinical trials so that KEYNOTE-671 matched the population of CheckMate-77T, nine parametric forms (exponential, accelerated failure time Weibull, proportional hazards Weibull, Gompertz, lognormal, loglogistic, gamma, generalized gamma and M-spline) were fit to the data. Model fit in the full network was assessed using the model fit statistics, visual inspection, and clinical plausibility. The 4-knot M-spline model was considered the top-fitting M-spline model, and was applied to the full network of evidence. The EFS HR estimates over 60 months were derived from the selected 4-knot M-spline PH ML-NMR model (Table 20). The results for the comparison between perioperative nivolumab and perioperative pembrolizumab were consistent with the standard NMA results, showing HRs [redacted] irrespective of time (HR, [redacted]; 95% CrI, [redacted]).

Table 20. Event-free survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the multilevel network meta-regression

Time	HR (95% CrI)
6	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]
30	[redacted]
36	[redacted]
42	[redacted]
48	[redacted]
54	[redacted]
60	[redacted]

CrI = credible interval; HR = hazard ratio.

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Sensitivity analyses (Table 22) conducted showed that the unadjusted HR estimate was slightly above the null value, whereas the base-case adjusted estimate was slightly below it. Findings were robust to different covariates included in the model and the missing data on PD-L1 expression level. Alternate PH parametric models yielded similar point estimates to the base-case model, although the lognormal model estimates were slightly above the null value. Non-PH parametric fits showed trends of increasing HRs over time, to varying degrees.

With respect to OS, the selected model was a 1-knot M-spline PH ML-NMR model.

Table 21 presents the numerical OS HR estimates of perioperative nivolumab versus perioperative pembrolizumab over 60 months. The comparison between perioperative nivolumab and perioperative pembrolizumab showed that HRs are very stable over time [redacted] over 60 months (HR, [redacted]; 95% CrI, [redacted]), with CrIs [redacted], demonstrating the similarity in OS.

It is important to note that, for the OS ML-NMR, the results presented here are included for completeness. Due to the short time between database lock and submission date, methodological descriptions specific to the OS analysis are not available in the appendix, as they are for other analyses. Nonetheless, we considered it beneficial to include the results at this stage to aid decision-making as much as possible.

Table 21. Overall survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the multilevel network meta-regression

Time	HR (95% CrI)
6	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]
30	[redacted]
36	[redacted]
42	[redacted]
48	[redacted]
54	[redacted]
60	[redacted]

CrI = credible interval; HR = hazard ratio.

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Table 22. Results across sensitivity analyses: hazard ratios for periadjuvant nivolumab + neoadjuvant chemotherapy versus periadjuvant pembrolizumab + neoadjuvant chemotherapy event-free survival

Sensitivity analysis type[a]	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months	60 months
Main model (spline PH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted (spline PH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Covariate inclusion (full)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric fit (lognormal PH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric fit (loglogistic PH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric fit (Weibull PH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric fit (lognormal NPH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric fit (loglogistic NPH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric fit (Weibull NPH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ITC = indirect treatment comparison; NPH = non–proportional hazards; PH = proportional hazards.

[a] The result for the main model (spline PH) was derived based on pairwise comparison between perioperative nivolumab and perioperative pembrolizumab within the broader core analysis of the ITC. For the sensitivity analysis, results were estimated using the broader ITC, which is considered reflective of the relative treatment effect between perioperative nivolumab and perioperative pembrolizumab.

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B.3.8.4 Uncertainties in the indirect and mixed treatment comparisons

A key strength of this ITC is the different analytical approaches taken for establishing the comparative effectiveness of perioperative nivolumab relative to perioperative pembrolizumab for stage II-IIIB resectable NSCLC, in turn addressing different objectives and features of the evidence base. Standard Bayesian NMA remains the simplest and most widely used method but relies on an assumption of PHs; the FP-NMA introduced time-dependent modelling of treatment effects. Importantly, for both EFS and OS, the top fitting FP-NMA model was a time-constant HR model, and the selected time-varying model had comparable goodness-of-fit, suggesting the models are equivalent from a statistical perspective. Therefore, the only reason to select the time-varying model would be to satisfy an a priori standpoint. A third approach, using a novel population-adjusted NMA implementation (ML-NMR) helped address population imbalances on potential treatment effect modifiers across the network.

This ITC is associated with several other strengths that are worth highlighting. First, the analysis was informed by a comprehensive SLR that captured all relevant evidence on the efficacy and safety of therapies evaluated among patients with resectable NSCLC. Another key strength is that reported analyses were rigorously conducted following best practice guidelines for the conduct of NMAs set forth by the NICE Decision Support Unit (DSU).[41]

There are also limitations associated with the ITC. An important limitation relates to the sparseness of the evidence base informing our base-case NMA. The sparseness of the evidence led to insufficient evidence to estimate the between-study standard deviation with enough precision; while priors were informed using evidence from larger networks, the uncertainty remained implausibly large and precluded consideration of the random effects model across analyses conducted. However, this limitation is addressed with the provision of other ITCs, notably, including the population-matched ML-NMR, which is considered methodologically rigorous. Second, with regards to AEs, a limitation of the current synthesis was the lack of meta-analysed indirect comparisons of AE rates between treatment regimens**.** Quantitative synthesis of safety data was not conducted, as it was considered inappropriate given the sparseness of the data. This limitation is expected to have a marginal impact on the final similarity in costs and effectiveness between nivolumab and pembrolizumab.

B.3.9 Adverse reactions

B.3.9.1 CheckMate-77T

The safety profile of the perioperative nivolumab group was consistent with the previously reported safety profile of the component agents (nivolumab and the chemotherapy agents used) in patients with NSCLC [redacted] (Table 23).[5]

The overall frequency of AEs was similar between the 2 treatment arms. Overall, the frequencies of serious AEs and AEs leading to discontinuation were [redacted] in the nivolumab arm than the chemotherapy arm. [redacted] due to study drug toxicity

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occurred in the nivolumab arm ([redacted]). Adverse events of any grade that were determined by the investigator to be related to the trial treatment (treatment-related AEs]) occurred in [redacted] of patients in the nivolumab group and in [redacted] in the chemotherapy group, with grade 3 or 4 treatment-related AEs occurring in [redacted] and [redacted] of patients, respectively.

In the nivolumab arm, the following grade 5 events occurred: [redacted]. In the placebo arm, grade 5 events included [redacted].[5]

Table 23. Safety profile

Event	Nivolumab (N = 228)			Chemotherapy (N = 230)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
All AEs (all causality), n (%)	[redacted]					
Treatment-related AEs, n (%)	[redacted]					
All AEs leading to discontinuation, n (%)	[redacted]					
All serious AEs, n (%)	[redacted]					
Surgery related AE,[a] n = 178 in each arm, n (%)	[redacted]					

AE = adverse event.

[redacted]

Source: BMS data on file (2025)[5]

B.3.9.2 NADIM-II

The safety profile of the perioperative nivolumab group was consistent with the previously reported safety profile of the component agents (nivolumab and the chemotherapy agents used) in patients with NSCLC. Adverse events of any grade that occurred during neoadjuvant treatment were reported in 50 patients (88%) in the nivolumab group and in 26 (90%) in the chemotherapy group. Grade 3 or 4 AEs occurred during neoadjuvant treatment in 11 patients (19%; some patients had events of both grades) and 3 patients (10%), respectively (Table 24).

Febrile neutropenia and diarrhoea were the most common grade 3 or 4 AEs in the nivolumab group (5% and 4% of patients, respectively). Treatment-related AEs of any grade that led to discontinuation of neoadjuvant treatment occurred in 5 patients (4 in the nivolumab group and 1 in the chemotherapy group). No delays in surgery due to AEs were noted.

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Table 24. Adverse events that occurred during neoadjuvant treatment

	Nivolumab plus chemotherapy (N = 57)			Chemotherapy alone (N = 29)		
Event	**Grade 1 or 2**	**Grade 3**	**Grade 4**	**Grade 1 or 2**	**Grade 3**	**Grade 4**
Any AEs (all causality), n (%)	50 (88)	10 (18)	2 (4)	26 (90)	3 (10)	0

AE = adverse event.

Source: Provencio et al. (2023)[36]

Adverse events of any grade that occurred during adjuvant treatment were reported in 57% of patients in the experimental arm. Grade 3 or 4 AEs that occurred during adjuvant treatment were reported in 5% of patients.

B.3.10 Conclusions about comparable health benefits and safety

Perioperative nivolumab is similar to perioperative pembrolizumab in the following aspects:

- Mechanism of action: Both nivolumab and pembrolizumab are PD-1 inhibitors.
- Treatment regimen: Both nivolumab and pembrolizumab are used in combination with chemotherapy for 4 cycles before surgery and as monotherapy for 1 year after surgery.
- Patient population: patient characteristics were similar in CheckMate-177 and KEYNOTE-671.
- EFS results: The EFS estimates for perioperative nivolumab were comparable with those for perioperative pembrolizumab (HR, [redacted]; 95% CrI, [redacted]) in the standard/traditional Bayesian NMA. The FP-NMA and ML-NMR results were consistent with the standard NMA results.
- OS results: The OS estimates for perioperative nivolumab were [redacted] those for perioperative pembrolizumab [redacted] in the standard NMA. In the time-varying OS analysis (FP-NMA), HRs numerically favoured perioperative nivolumab at earlier timepoints over perioperative pembrolizumab but trended towards 1 over time ([redacted]). In the ML-NMR, [redacted] over 60 months [(HR, [redacted]; 95% CrI, [redacted]), with [redacted] all evaluated timepoints suggesting similar OS for perioperative nivolumab and perioperative pembrolizumab.

Overall, the interpretation for the ITC result for EFS remained consistent among the 3 NMA methods, indicating potential equivalence of perioperative nivolumab and perioperative pembrolizumab. The ITC result for OS in the traditional NMA, FP-NMA, and ML-NMR indicate OS equivalence of these 2 regimens based on the evidence available to date.

Therefore, there is a robust rationale and evidence that perioperative nivolumab will have equivalent efficacy and safety to perioperative pembrolizumab, supporting the use of cost comparison for this appraisal.

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B.3.11 Ongoing studies

CheckMate-77T is ongoing, and further database locks are expected, to include testing of OS at final analysis (planned at approximately [redacted] events).

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B.4 Cost comparison analysis

B.4.1 Changes in service provision and management

The administration of perioperative nivolumab and perioperative pembrolizumab occurs in the same clinical setting, typically in secondary or tertiary care hospitals where patients receive chemotherapy and immunotherapy. There are no anticipated differences in the location or setting of care between the 2 treatments.

As outlined in Section B.3.8, the similarity in treatment effect over time for perioperative nivolumab and perioperative pembrolizumab has been demonstrated by the ITC conducted by BMS. As described in Section B.3.10, perioperative nivolumab is similar to perioperative pembrolizumab in the following aspects:

- Mechanism of action: Both nivolumab and pembrolizumab are PD-1 inhibitors.
- Treatment regimen: Both nivolumab and pembrolizumab are used in combination with chemotherapy for 4 cycles before surgery and as monotherapy for 1 year after surgery.
- Trial characteristics: Both CheckMate-77T and KEYNOTE-671 were phase 3, international, open-label, double-blinded studies. The median follow-up duration for both trials was 3.4 years.
- Risk of bias: Both CheckMate-77T and KEYNOTE-671 were assessed as having an overall low risk of bias.
- Patient population: CheckMate-77T included 461 patients under randomisation, whereas Keynote-671 included 797 patients. Similarities were observed in patient characteristics across the base-case studies of both trials.
- EFS results: The EFS estimates for perioperative nivolumab were comparable with those of perioperative pembrolizumab ([redacted]; 95% CrI, [redacted]) in the standard/traditional Bayesian NMA. The FP-NMA and ML-NMR results were consistent with the standard NMA results.
- OS results: The OS estimates for perioperative nivolumab were comparable with those of perioperative pembrolizumab (HR, [redacted]; 95% CrI [redacted]) in the standard NMA. In the time-varying OS analysis (FP-NMA), HRs [redacted]).

Given the similarity in CheckMate-77T and KEYNOTE-671 trial designs, it is assumed that all direct costs, except for the drug acquisition and administration costs, are equal. In the context of perioperative nivolumab and perioperative pembrolizumab, all patients receive either nivolumab or pembrolizumab during the neoadjuvant period in addition to a basket of platinum-doublet chemotherapy, which includes cisplatin, carboplatin, pemetrexed, gemcitabine, vinorelbine, docetaxel, and paclitaxel. For the analysis, it is assumed that the combination of chemotherapy received in the neoadjuvant setting is identical for both perioperative nivolumab and perioperative pembrolizumab. As a result, neoadjuvant chemotherapy costs will not affect the cost comparison between the 2 treatments. Therefore,

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neoadjuvant chemotherapy costs are not considered in the analysis. In other words, the only difference in resource use between perioperative nivolumab and perioperative pembrolizumab is defined by differences in nivolumab and pembrolizumab drug acquisition and administration costs.

B.4.2 Cost comparison analysis inputs and assumptions

B.4.2.1 Features of the cost comparison analysis

The drug acquisition and administration costs are estimated based on the assumption that all patients will receive a full course of treatment for both perioperative nivolumab + neoadjuvant chemotherapy or perioperative pembrolizumab + neoadjuvant chemotherapy. This assumption is grounded in the rationale that the treatment effect of both perioperative nivolumab and perioperative pembrolizumab is assumed to be similar, resulting in an equal duration of therapy for both treatments. Consequently, the full course of treatment is used in the analysis.

B.4.2.2 Intervention and comparators' acquisition costs

The cost of perioperative treatment includes both pre-surgical and post-surgical treatments. Specifically, the cost of neoadjuvant treatment accounts for the drugs administered before surgery, whereas the cost of adjuvant treatment covers the drugs administered after surgery. The inputs used to estimate these costs are summarised in Table 25. The unit drug cost for nivolumab and pembrolizumab is sourced from the Monthly Index of Medical Specialities–UK Drug Database.[42]

The relative treatment intensity of pembrolizumab is unknown, therefore this analysis assumes that all nivolumab and pembrolizumab patients get the per-protocol course of treatment, i.e., the percentage of patients on treatment each cycle for perioperative nivolumab and perioperative pembrolizumab will be the same (i.e., 100%).

The dosing regimens for nivolumab in the perioperative setting were based on those used in CheckMate-77T. In the neoadjuvant phase, nivolumab at a dose of 360 mg is administered every 3 weeks (Q3W), in combination with chemotherapy, for up to 4 cycles prior to surgery. In the adjuvant phase, following surgery, trial participants receive nivolumab at a dose of 480 mg every 4 weeks, for up to 1 year (13 cycles).

For pembrolizumab, in the neoadjuvant setting, dosing was aligned with the regimen used in the KEYNOTE-671 trial. In KEYNOTE-671, in the neoadjuvant phase, pembrolizumab was administered at a dosage of 200 mg Q3W, in combination with chemotherapy, for 4 cycles prior to surgery. After surgery, clinical trial participants could receive up to 13 cycles of adjuvant pembrolizumab monotherapy at a fixed dose of 200 mg Q3W. Alternatively, pembrolizumab could be administered at a fixed dose of 400 mg every 6 weeks (Q6W), which is the preferred regimen among clinicians in the adjuvant setting.[2] Therefore, in accordance with NICE TA1017, it is assumed that patients in the adjuvant setting receive 1 cycle of pembrolizumab 200 mg, followed by 6 cycles of 400 mg Q6W.

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Table 25. Acquisition costs of the perioperative nivolumab and perioperative pembrolizumab

	Perioperative nivolumab		Perioperative pembrolizumab	
	Neoadjuvant	**Adjuvant**	**Neoadjuvant**	**Adjuvant**
Pharmaceutical formulation	10 mg/mL		100 mg	
(Anticipated) care setting	Neoadjuvant	Adjuvant	Neoadjuvant	Adjuvant
Acquisition cost (excluding VAT)[a]	£439 per vial (with vial volume of 4 mL)		£2,630 per pack	
Method of administration	IV			
Doses	360 mg	480 mg	200 mg	200 mg (initial cycle)[b] 400 mg (subsequent cycles)[b]
Dosing frequency	Q3W	Q4W	Q3W	Q6W
Dose adjustments	NA	NA	NA	NA
Average length of a course of treatment	3 weeks	4 weeks	3 weeks	6 weeks
Average cost of a course of treatment (acquisition costs only)	£3,951	£5,268	£5,260	£5,260 (initial cycle)[b] £10,520 (subsequent cycles)[b]
(Anticipated) average interval between courses of treatment	NA	NA	NA	NA
(Anticipated) number of repeat courses of treatment	4	13	4	7[b]

IV = intravenous; QxW = every x weeks; VAT = value-added tax; NA = not applicable.

[a] The acquisition cost is list price.

[b] Patients in the adjuvant setting will receive 1 cycle of pembrolizumab 200 mg followed by a maximum of 6 cycles of a 400 mg dose Q6W.

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B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

Drug administration costs were applied per administration for drugs administered intravenously. Unit costs for drug administration were derived from NHS England (2024)[43] and are summarised in Table 26**,** along with the administration cost per treatment cycle (course of a treatment) for perioperative nivolumab and perioperative pembrolizumab.

In NICE TA1017,[2] SB13Z HRG code is used for pembrolizumab and nivolumab in the neoadjuvant phase (when administered in combination with chemotherapy) and SB12Z HRG code in the adjuvant phase. As noted in that submission, this is in line with the approach advised by the Cancer Drugs Fund lead in a pembrolizumab submission.[44] Therefore, in alignment with NICE TA1017,[2] in this analysis, SB13Z and SB12Z codes are used in the neoadjuvant and adjuvant phases, respectively, for both perioperative nivolumab and perioperative pembrolizumab.

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Table 26. Resource costs of the intervention and comparator technologies

	Perioperative nivolumab	Perioperative pembrolizumab
Deliver more complex parenteral chemotherapy at first attendance (neoadjuvant period)		
Unit cost		
Cost (£), price year	£190.69	£190.69
Source reference	National Cost Collection for the NHS (2024) [43]	National Cost Collection for the NHS (2024)[43]
Rationale for source	NHS cost with currency code SB13Z	NHS cost with currency code SB13Z
Units per course of treatment	1 for neoadjuvant period	1 for neoadjuvant period
Number of units	4	4
Source reference	NA	NA
Rationale for source	Administration for nivolumab and chemotherapy at the same time for first attendance	Administration for pembrolizumab and chemotherapy at the same time for first attendance
Total cost to deliver more complex parenteral chemotherapy at first attendance		
Per course of treatment	£190.69	£190.69
Over the full time horizon	£762.76	£762.76
Deliver simple parenteral chemotherapy at first attendance (adjuvant period)		
Unit cost		
Cost (£), price year	£138.10	£138.10
Source reference	National Cost Collection for the NHS (2024)[43]	National Cost Collection for the NHS (2024)[43]
Rationale for source	NHS cost with currency code SB12Z	NHS cost with currency code SB12Z
Units per course of treatment	1 for adjuvant period	1 for adjuvant period
Number of units	13	7
Source reference	NA	NA
Rationale for source	Administration for first attendance	Administration for first attendance

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	Perioperative nivolumab	Perioperative pembrolizumab
Total cost of deliver simple parenteral chemotherapy at first attendance		
Per course of treatment	£138.10	£138.10
Over the full time horizon	£1,795.34	£966.72

NA = not applicable; NHS = National Health Service.

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B.4.2.4 Adverse reaction unit costs and resource use

As mentioned in Section B.4.1, given the similar treatment effect between perioperative nivolumab and perioperative pembrolizumab, it is assumed that direct costs, including AE management and disease management costs, are equivalent for both treatments. Therefore, these costs are excluded from the cost comparison analysis.

B.4.2.5 Miscellaneous unit costs and resource use

As mentioned in Section B.4.1, given the similar treatment effect between perioperative nivolumab and perioperative pembrolizumab, it is assumed that direct costs, including AE management and disease management costs, are equivalent for both treatments. Therefore, these costs are excluded from the cost comparison analysis.

B.4.2.6 Clinical expert validation

Not applicable.

B.4.2.7 Uncertainties in the inputs and assumptions

Not applicable.

B.4.3 Base-case results

The base-case results for the comparison of perioperative nivolumab against perioperative pembrolizumab at list price are presented in Table 27. Base-case results are estimated based on the assumption that all patients complete the full course of treatment. No discounting was applied in the analysis.

Table 27. Base-case results

	Acquisition costs	Administration costs	TOTAL COSTS	Difference
Perioperative nivolumab	£84,288.00	£2,558.10	£86,846.10	−£4,303.38
Perioperative pembrolizumab	£89,420.00	£1,729.48	£91,149.48	

B.4.4 Sensitivity and scenario analyses

Not applicable.

B.4.5 Subgroup analysis

No subgroup analyses have been explored since the label population matches that for pembrolizumab.

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B.4.6 Interpretation and conclusions of economic evidence

The list price comparison of perioperative nivolumab + neoadjuvant chemotherapy against perioperative pembrolizumab + neoadjuvant chemotherapy yielded incremental cost-saving of −£4,303.38. The results of this analysis suggest that, given the similar treatment effects between perioperative nivolumab and perioperative pembrolizumab, perioperative nivolumab is associated with lower total costs at list price. However, BMS acknowledge that the patient access scheme (PAS) for nivolumab and PAS for pembrolizumab may influence the similarity in net price for perioperative nivolumab and perioperative pembrolizumab. [redacted].

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B.5 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost comparison appraisal

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non–small cell lung cancer [ID6310]

Summary of Information for Patients (SIP)

File name	Version	Contains confidential information	Date
ID6310 Nivolumab perioperative NSCLC SIP [CON]	1.0	Yes	22 April 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic: Nivolumab Brand: Opdivo®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults, aged 18 years and above, with resectable (this means it can be removed by surgery) non–small cell lung cancer (NSCLC).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The marketing authorisation is for the following: • To start, nivolumab is used in combination with chemotherapy as a neoadjuvant treatment (this means it is used before surgery). • Then, nivolumab is continued on its own as an adjuvant treatment (this means it is given after surgery). Together, this is known as a perioperative treatment. Perioperative nivolumab for the treatment of adults with resectable NSCLC received its marketing authorisation in the United Kingdom (UK) from the Medicines and Healthcare products Regulatory Agency (MHRA) on 27 February 2025. The marketing authorisation can be found here: https://mhraproducts4853.blob.core.windows.net/docs/94f75cd2f341119d67cec446e2d8161ebdbf8bf8

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

BMS has previously collaborated with Roy Castle Lung Cancer Foundation (RCLCF) to gain insight into the patient perspectives associated with lung cancer diagnosis and disease management.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Lung cancer is the most common cancer worldwide, and it is the leading cause of cancer deaths, both worldwide and in the UK.[1-3] Data from England show that, in 2022[4]:

- Approximately 36,886 people were diagnosed with lung cancer[4]
- Of these, approximately 90% were known or assumed to have NSCLC
  - NSCLC is therefore the most common subtype of lung cancer and is defined as any type of lung cancer other than small cell lung cancer (both types are initially named based on how the cancer cells look under the microscope)[5]
  - The most common types of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma[5]

NSCLC can be classified by stage, where stages IA, IB, IIA, and IIB are considered early disease; stages IIIA, IIIB, and IIIC are considered locally advanced disease; and stage IV is considered metastatic disease (Table 1).[6]

Table 1. NSCLC classification[6]

Phase of disease	Definition	Stage(s)
Early disease	Cancer is found in the lungs or nearby lymph nodes but has not spread to other parts of the body	Stages IA, IB, IIA, and IIB
Locally advanced disease	Cancer has begun to spread further in the chest	Stages IIIA, IIIB, and IIIC
Metastatic disease	Cancer has spread to other parts of the body	Stage IV

People with stages I-III NSCLC are often able to have the cancer resected (removed by surgery), which may cure the disease. However, the cancer comes back for about 30%-55% of people and will eventually lead to death.

In England in 2022, less than half of people diagnosed with lung cancer were still alive 1 year after diagnosis.[4] The number of people still alive 5 years after diagnosis in the UK is generally below the European average.[7]

An unmet need exists for treatment options to improve survival for those with stages I-III NSCLC.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

People who are thought to have lung cancer will undergo a series of tests to confirm the diagnosis of lung cancer and determine the type of lung cancer and its stage. The following tests are recommended:[8-10]

- Physical examination and complete medical history
- Laboratory tests (complete blood count, kidney and liver function testing)
- Collection of a sample of tumour for biopsy
- Diagnostic imaging studies (CT scan, PET scan, MRI scan, X-ray)

Based on the results of these tests, a healthcare team decides on appropriate treatment.

No additional tests are required for the use of perioperative nivolumab + chemotherapy.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

NICE recommended treatment options for people with newly diagnosed, potentially resectable NSCLC include immunotherapy, surgery, radiotherapy, chemotherapy, or a combination of these.[8]

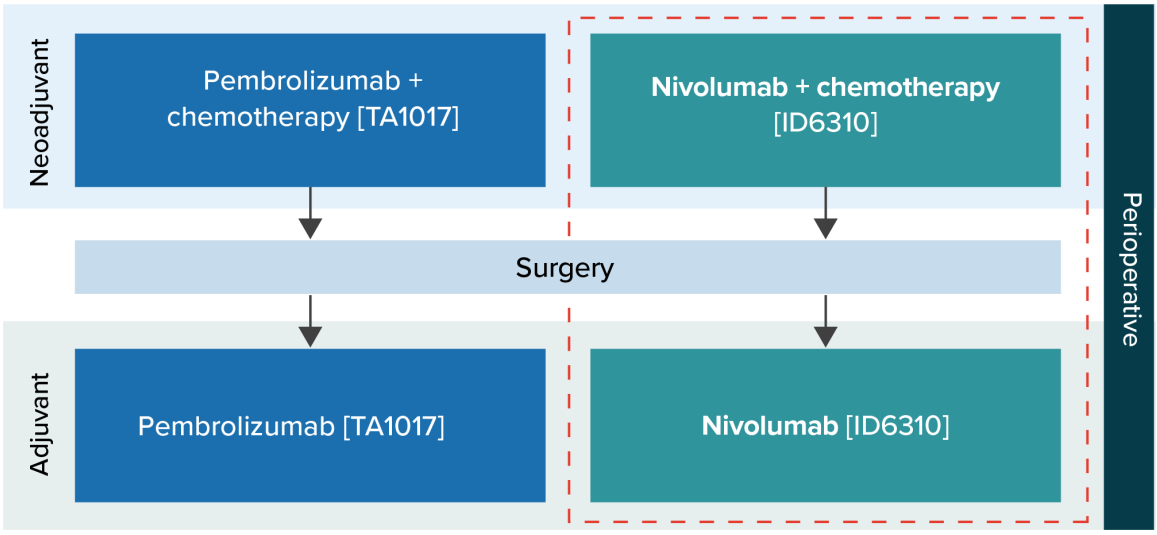
Immunotherapy with pembrolizumab (Keytruda) used perioperatively (before surgery with chemotherapy and after surgery on its own) recently became the standard of care for people with resectable NSCLC in England, following positive recommendation by NICE in 2024[11] and confirmed by 7 UK-based clinicians.

In addition, data on use of these medicines in early NSCLC highlight:

- Use of perioperative pembrolizumab (Keytruda) has been increasing since its approval.
- Use of neoadjuvant nivolumab (Opdivo) has reduced, reflecting the change in standard of care for people able to receive perioperative therapy.
- Perioperative durvalumab (Imfinzi) has not been widely used.

Perioperative nivolumab (outlined by the dashed red box in Figure 1) will be an additional perioperative treatment option available to people with resectable NSCLC). Perioperative nivolumab works in the same way as pembrolizumab.

Figure 1. Potential position of perioperative nivolumab + chemotherapy in the treatment pathway for resectable NSCLC in clinical practice in England and Wales



NSCLC = non–small cell lung cancer.

Sources: NICE (2024)[11]; NICE (2025)[12]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The published literature about NSCLC reports that tiredness, shortness of breath, pain, and cough are the most troublesome symptoms of stages I-III NSCLC (non-metastatic, i.e. NSCLC that has not spread to other parts of the body) that affect health-related quality of life both before and during treatment.[13-15]

A patient's quality of life can be significantly affected if the cancer comes back and spreads to other parts of the body (metastatic disease).[16-20] When this occurs, symptoms get worse, and can include:

- Bone pain and fracture (if cancer spreads to the bones)
- Headaches, seizures, and neurologic complications (if cancer spreads to the brain)

It's important to acknowledge that caregivers for people with NSCLC also experience a considerable burden associated with care, including increased distress (such as being anxious about an uncertain future with the patient with cancer), reductions in psychological and social well-being owing to disruption of self-care and lifestyle interference (e.g., limits in ability to participate in valued activities), as well as problems related to perceived demands of, and preparedness for, the

caregiver role.[21,22] Effective treatments can help reduce the burden on caregivers by preventing or delaying the development of metastatic disease.

Considering how effective treatments can prevent or delay the cancer from spreading (metastatic disease), these treatments could also prevent symptoms and health-related quality of life from worsening as well.

Ultimately, effective treatments can benefit both patients and caregivers in terms of reducing the overall burden of disease.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The immune system is made up of special proteins, cells, tissues, and organs. They work together to protect the body from harmful antigens (something that can trigger the immune system to respond) like bacteria, viruses, and parts of cancer cells.

T-cells are a type of white blood cell that can recognise and destroy harmful antigens. They are activated when needed and turned off when not needed through signals from other immune cells. These signals work like a lock and key system to control the immune response.

When normal cells turn into cancer cells, some of their surface markers change and can be seen as harmful by the immune system. However, cancer cells can hide from the immune system by using the same signals that usually turn off the immune response.

Nivolumab is a medicine that attaches to a receptor on T-cells called PD-1. This receptor can turn off T-cells. By blocking PD-1, nivolumab prevents T-cells from being turned off, boosting their activity and helping the immune system attack and destroy cancer cells.[23]

Nivolumab is given with chemotherapy before surgery (known as a neoadjuvant treatment). Nivolumab and chemotherapy each have different ways of working and have additional activity as combination therapy. Chemotherapy works by stopping cancer cells from growing and repairing themselves, which can lead to their death. When cancer cells die, they send signals that the immune system can detect and destroy. Examples of chemotherapy treatments include cisplatin, carboplatin, pemetrexed, docetaxel, and paclitaxel. Combining chemotherapy with nivolumab before surgery helps control cancer symptoms and tumour growth quickly. It also helps nivolumab work better in this setting. Using both treatments before surgery is beneficial because the immune system is stronger before surgery, making it easier to fight the cancer. Additionally, using nivolumab and chemotherapy before surgery ensures the cancer gets treated in time and makes the tumour easier to remove. Having only 4 cycles of each treatment reduces the side effects and avoids delays in surgery.[24-27] Using only nivolumab for up to 1 year after surgery minimises adverse events while reducing risk of recurrence.

Nivolumab + chemotherapy summary of product characteristics:
https://www.medicines.org.uk/emc/product/6888

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

▪ Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
This request includes a combination (nivolumab + chemotherapy); please see 3a for information on how these treatments work together.

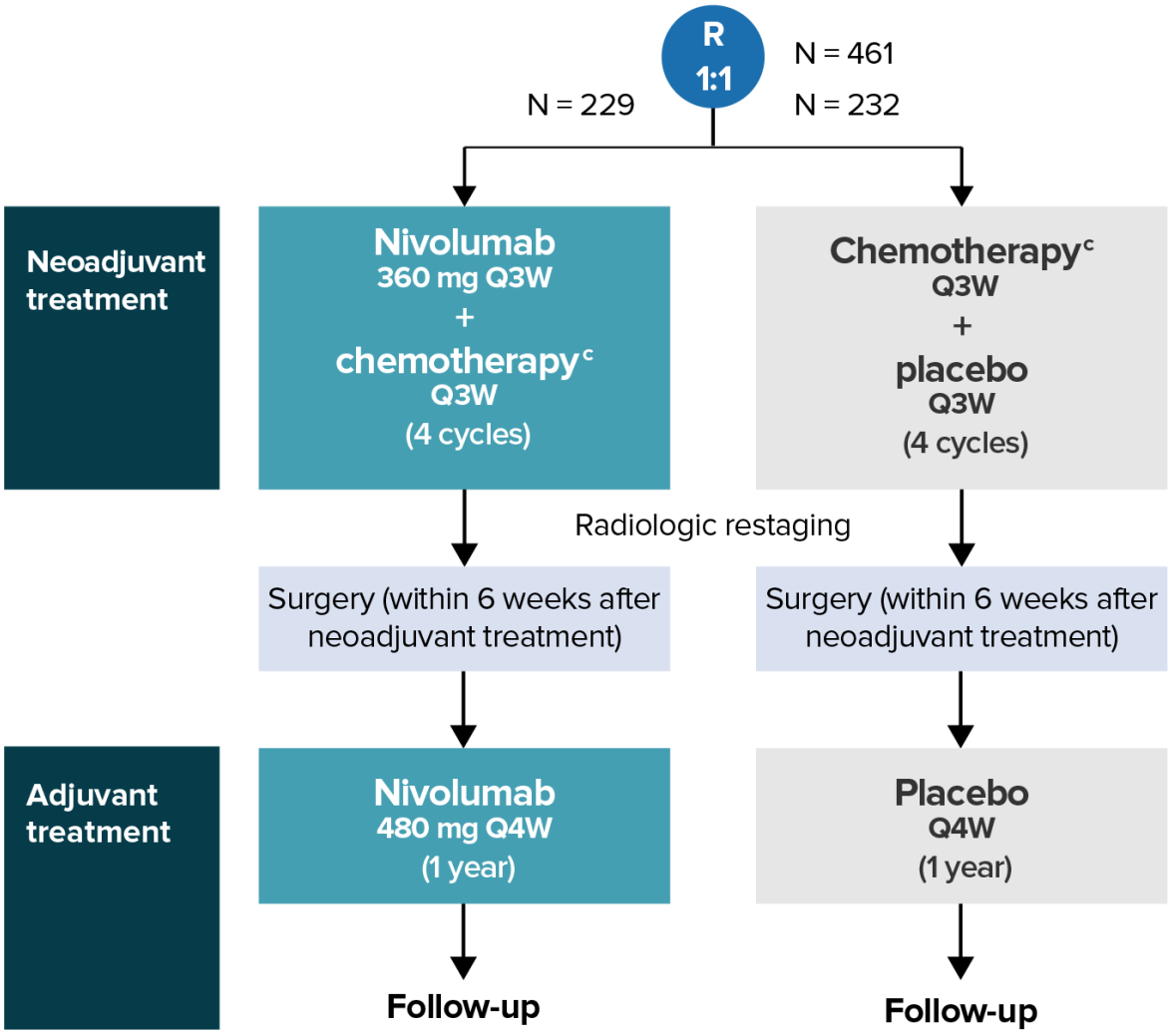
3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Both nivolumab and chemotherapy (such as cisplatin, carboplatin, pemetrexed, docetaxel, and paclitaxel) are given by injection into a vein. This usually takes place in an outpatient hospital setting.[28] When given before surgery, neoadjuvant nivolumab is administered as a 360 mg dose, along with chemotherapy. Both are given together every 3 weeks for up to 4 cycles. When given after surgery, adjuvant nivolumab is administered alone (monotherapy) as a 480 mg dose every 4 weeks for up to 13 cycles (1 year). It is not expected that the dosing or administration method of perioperative nivolumab would greatly affect patients or caregivers compared with giving perioperative pembrolizumab, considering their similarity.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
CheckMate-77T is the main clinical trial used in this appraisal. It includes people with resectable stage II-IIIB NSCLC. It aims to evaluate how well perioperative (before and after surgery) nivolumab plus chemotherapy works compared with placebo plus neoadjuvant chemotherapy. A total of 461 participants were randomised (229 to the perioperative nivolumab group and 232 to the neoadjuvant chemotherapy group),[29] as shown in Figure 2.

Figure 2. CheckMate-77T trial design



1:1 = 1-to-1 ratio; Q3W = every 3 weeks; Q4W = every 4 weeks; R = randomisation.

Note: radiological restaging means reassessing the stage of the tumour following surgery.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The following outcomes are the main ones used to find out how well perioperative nivolumab works, compared with neoadjuvant chemotherapy.

Event-Free Survival: This assesses the amount of time that participants are free from an "event" (of disease progression, worsening of disease, or death due to any cause) from the start of the trial.

- Fewer people had events in the perioperative nivolumab group than in the neoadjuvant chemotherapy group (Figure 3)
  - Perioperative nivolumab: 88 of 229 participants, or 38.4%

– Neoadjuvant chemotherapy: 124 of 232 participants, or 53.4%

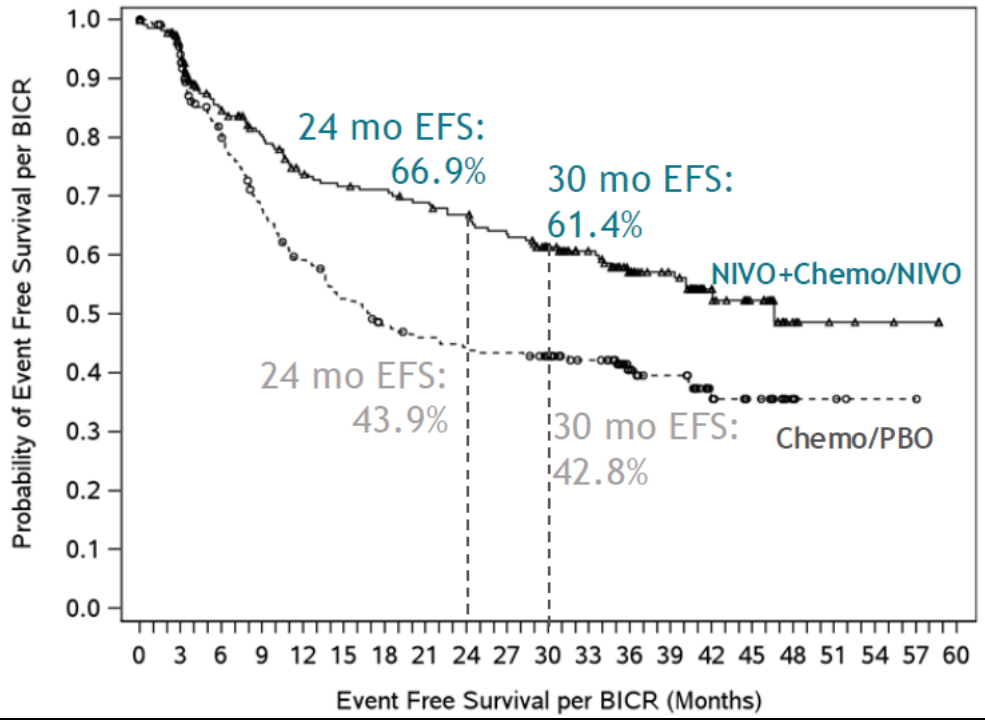
- The hazard ratio for event-free survival was 0.61 (95% confidence interval[a] = 0.46-0.80), which means that the risk of the cancer coming back, progressing, or the person dying of any cause is 39% lower in people receiving perioperative nivolumab compared with neoadjuvant chemotherapy.
- Median[b] event-free survival (the time taken for half of the people in the study to experience an event) was longer in the perioperative nivolumab group than in the neoadjuvant chemotherapy group.
  – Perioperative nivolumab: median = 46.6 months; 95% confidence interval = 35.8 to not reached[c]
  – Neoadjuvant chemotherapy: median = 16.9 months; 95% confidence interval = 13.6-28.2

[a] The 95% confidence interval presents 2 values; there is a 95% chance that the true population results lie between these 2 values.

[b] Median is a way to find the middle value in a set of numbers.

[c] Not reached in the upper bound value of the confidence interval means some participants in the perioperative nivolumab group were still event free at the time of the analysis.

Figure 3. Event-free survival



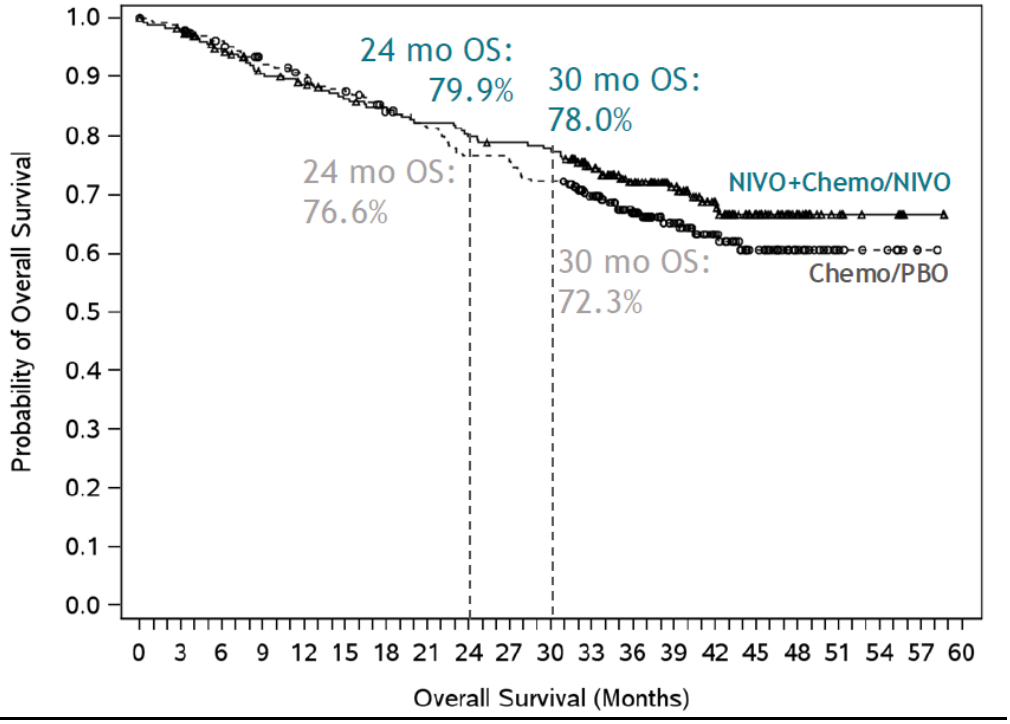
BICR = Blinded Independent Central Review; Chemo = chemotherapy; EFS = event-free survival; mo = month; NIVO = nivolumab; PBO = placebo.

Overall Survival: This assesses how long participants live from the start of the trial.

- Fewer people died of any cause in the perioperative nivolumab group than in the neoadjuvant chemotherapy group (Figure 4)
  – Perioperative nivolumab: 64 people, or 27.9%
  – Neoadjuvant chemotherapy: 76 people, or 32.8%
  – The hazard ratio for overall survival was 0.85 (95% confidence interval = 0.61-1.18), which means the risk of death was 15% lower in the perioperative nivolumab group than the neoadjuvant chemotherapy group.

- Median overall survival (the time that half of participants in the study have died and half are alive) was not reached for either group. This means that more than half of the study participants in both groups were alive at the time of analysis, and so median overall survival is undefined.

Figure 4. Overall survival



Chemo = chemotherapy; NIVO = nivolumab; OS = overall survival; PBO = placebo.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the CheckMate-77T trial, participants filled out the EQ-5D-3L questionnaire. This commonly used questionnaire is a simple way to measure how treatments could affect the participant's quality of life. EQ refers to the group that developed it (EuroQol), 5D refers to the 5 parts of health that it measures (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), 3L means that each of the 5 parts of health measured has 3 levels (no problems, some problems, extreme problems).

At the start of the trial, mean (average) scores on the questionnaire were similar for participants in the perioperative nivolumab group and the neoadjuvant chemotherapy group. Both groups experienced a small improvement in their health scores after treatment.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Table 2 summarises the side effects (adverse events) reported in the CheckMate-77T trial. Overall, the safety and side effects reported by participants in the trial are similar to the known side effects of treatment with nivolumab and chemotherapy.

Table 2. Safety summary of CheckMate-77T

	Perioperative nivolumab (N = 228)	Neoadjuvant chemotherapy (N = 230)
Any adverse event	222 (97%)	225 (98%)
Adverse events resulting in stopping treatment	57 (25%)	25 (11%)
Deaths due to study drug toxicity	2 (0.9%)	0

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The main benefits for people receiving perioperative nivolumab are expected to be similar to those of perioperative pembrolizumab. For example, for both treatments, the main benefits are:

- Reducing the risk of the cancer coming back
- Preventing the disease from progressing to a stage where treatments to cure the disease are not available

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The disadvantages to people receiving perioperative nivolumab are expected to be similar to those of perioperative pembrolizumab. For example, side effects (which are usually mild to moderate in severity) and an increased risk of immune-related side effects, some of which may last even after the end of treatment. Clear guidance is provided to healthcare providers on how to manage these side effects.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The value and economic considerations of perioperative nivolumab are likely to be similar to those of perioperative pembrolizumab. For example, the administration of perioperative nivolumab and perioperative pembrolizumab occurs in the same clinical setting in hospitals; therefore, no differences are expected in the location or setting of care between the 2 treatments.

The main difference between perioperative nivolumab and perioperative pembrolizumab is likely to be the cost of buying the drugs and cost of appointments needed to give the drugs to people with NSCLC:

- Nivolumab is given as a 360 mg dose every 3 weeks for up to 4 cycles before surgery, and as a 480 mg dose every 4 weeks for up to 13 cycles (about 1 year).
- Pembrolizumab is given as a 200 mg dose every 3 weeks for up to 3 cycles before surgery, and as a 200 mg dose every 3 weeks for up to 13 cycles (about 1 year) or as a 400 mg dose every 6 weeks for up to 1 year.

A comparison with pembrolizumab was performed to compare differences between the 2 treatments. Overall, the comparison showed that both treatments have similar efficacy, and therefore no economic impact is expected.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Perioperative pembrolizumab is the standard of care for treating people with stage I-III NSCLC. Perioperative nivolumab is a very similar treatment and will offer an alternative option for treating NSCLC before and after surgery, to enable more people to remain disease free.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equalities issues are anticipated.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on NICE and the role of patients**:** ▪ Public involvement at NICE: Public involvement | NICE and the public | NICE Communities | About | NICE ▪ NICE's guides and templates for patient involvement in health technology assessments: Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE ▪ EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ ▪ EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf ▪ National Health Council Value Initiative: https://nationalhealthcouncil.org/issue/value/ ▪ INAHTA: http://www.inahta.org/ ▪ European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adjuvant: Treatment given after the main treatment to help prevent the cancer from coming back **Adverse event:** An unwanted side effect (such as rash, sickness, pain) **Antigen:** something that can trigger the immune system to respond—like bacteria, viruses, and parts of cancer cells **CT (computed tomography) scan:** Passes X-rays through the body to create detailed images of the inside of the body **EQ-5D-3L:** A questionnaire to measure health-related quality of life. EQ refers to the group that developed it (EuroQol), 5D refers to the 5 parts of health that it measures (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), 3L means that each of the 5 parts of health measured has 3 levels (no problems, some problems, extreme problems) **MRI (magnetic resonance imaging) scan:** uses strong magnetic fields and radio waves to produce detailed images of the inside of the body **Neoadjuvant:** Treatment given before the main treatment (like surgery) to shrink the tumour **Perioperative:** Treatment given before and after the surgery **PET (positron emission tomography) scan**: Uses a small amount of radiation to produce detailed images of the inside of the body **Placebo**: A substance that looks like a medicine but isn't one and contains no active ingredients

Resectable: A tumour that can be removed by surgery

X-ray: A method using small amounts of radiation to obtain detailed images of the inside of the body

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6310]

Clarification questions

August 2025

File name	Version	Contains confidential information	Date
ID6310 clarification questions responses (CON)	1.0	Yes	02.09.2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Indirect treatment comparisons

A1. Priority question. Please provide full working code and data files for the indirect treatment comparisons (ITCs) reported in the company submission to enable validation.

The working code and data files are available in the subfolders attached:

- Bayesian network meta-analysis (NMA) code and data files: "*NMA code files*"
    - Within the subfolder entitled "Data files", two sets of data are provided: one with the subnetwork from the original submission (KEYNOTE-671 [KN671], NADIM II and CheckMate 77T [CM77T], entitled "KN671 NADIM II CM77T") and one from the new subnetwork requested in the responses below (KN671, AEGEAN and CM77T, entitled "KN671 AEGEAN CM77T")
- Fractional polynomial NMA (FP-NMA) code and data files: "*FP code files*"
    - Within the subfolder entitled "Data files", two sets of data are provided: one with the network from the original submission (see response to question A5, folder entitled "KN671, NADIM II and CM77T") and one from

the new subnetwork requested in the responses below (KN671, AEGEAN and CM77T, entitled “subnetwork”)

- Multi-level network meta-regression (ML-NMR) code and data files: “*ML-NMR code files*”
    - Due to confidentiality reasons, we are unable to share the individual patient data (IPD) that was used in the ML-NMR. However, we have provided the full working code to conduct the ML-NMR, the aggregate-level data files, and sufficient detail on data processing steps and model specification that would allow the EAG to reproduce the analyses if they had IPD access.

A2. Priority question. Please provide:

a) **details of the survival curve selection used in the multilevel network meta-regression (ML-NMR) and demonstrate that the selected curve has a good fit to the baseline hazard (and a good visual fit).**
b) **model convergence plots and model fit statistics for all of the ITCs conducted in the company submission.**

Response to Question A2a):

As described in the original NICE submission (**Appendix Section 2.3.4** and **Section 2.4** of the original submission), model selection was conducted using the broader network of evidence (**Figure 82** in original submission). Explorations on knot number and location were fit to the subset of trials for which full IPD were available and exploration of other parametric forms were conducted on the full network. For the restricted network of evidence (**Figure 83** in original submission), visual inspection and statistical goodness-of-fit were reviewed to confirm the choice of model.

Event-free survival (EFS)

The figures that follow depict the modelled baseline hazards and survival curves from the selected model (4-knot M-Spline proportional hazards model), as well as the other models that had been candidates based on goodness-of-fit statistics. First, the IPD-based assessments of knot placement are provided, from which the 4-knot model was preferred as it appeared to capture sufficient flexibility while not over-fitting the early shape of the curve as seen in the 5-knot model (**Figure 1** for proportional hazards models, and **Figure 2** for non-proportional hazards models).

Next, the visualizations of the 4-knot M-Spline model compared with other top-fitting parametric forms are provided in **Figure 3** and **Figure 4**. The visual inspection of these hazard plots showed that the functional forms of the lognormal and loglogistic models

led to constraints that were not evident in the 4-knot M-Spline model, further supporting the choice of the flexible parametric 4-knot M-Spline model.

In **Figure 5** and **Figure 6**, the Kaplan-Meier curves from each trial are overlaid against the modelled output from the ML-NMR specific to the target population of each trial. Note that the modelled output of periNIVO+neoCT represents the meta-analysed estimate using both the CM77T and NADIM II evidence, which is more heavily weighted by the CM77T evidence base; thus, some degree of deviation between the NADIM II Kaplan-Meier curves and modelled outputs is reasonable.

Note that empirical baseline hazards are best depicted using a smoothing algorithm; hence the hazard plots were simply interpreted alongside the survival curves with Kaplan-Meier curve overlays.

Figure 1 Visual inspection of EFS hazards and survival curves from proportional-hazard M-Spline-based models having different number of knots

Figure 2 Visual inspection of EFS hazards and survival curves from non-proportional-hazard M-Spline-based models having different number of knots

Figure 3 Visual inspection of EFS hazards and survival curves from top proportional-hazard candidate models (based on goodness-of-fit statistics) (full network of evidence)

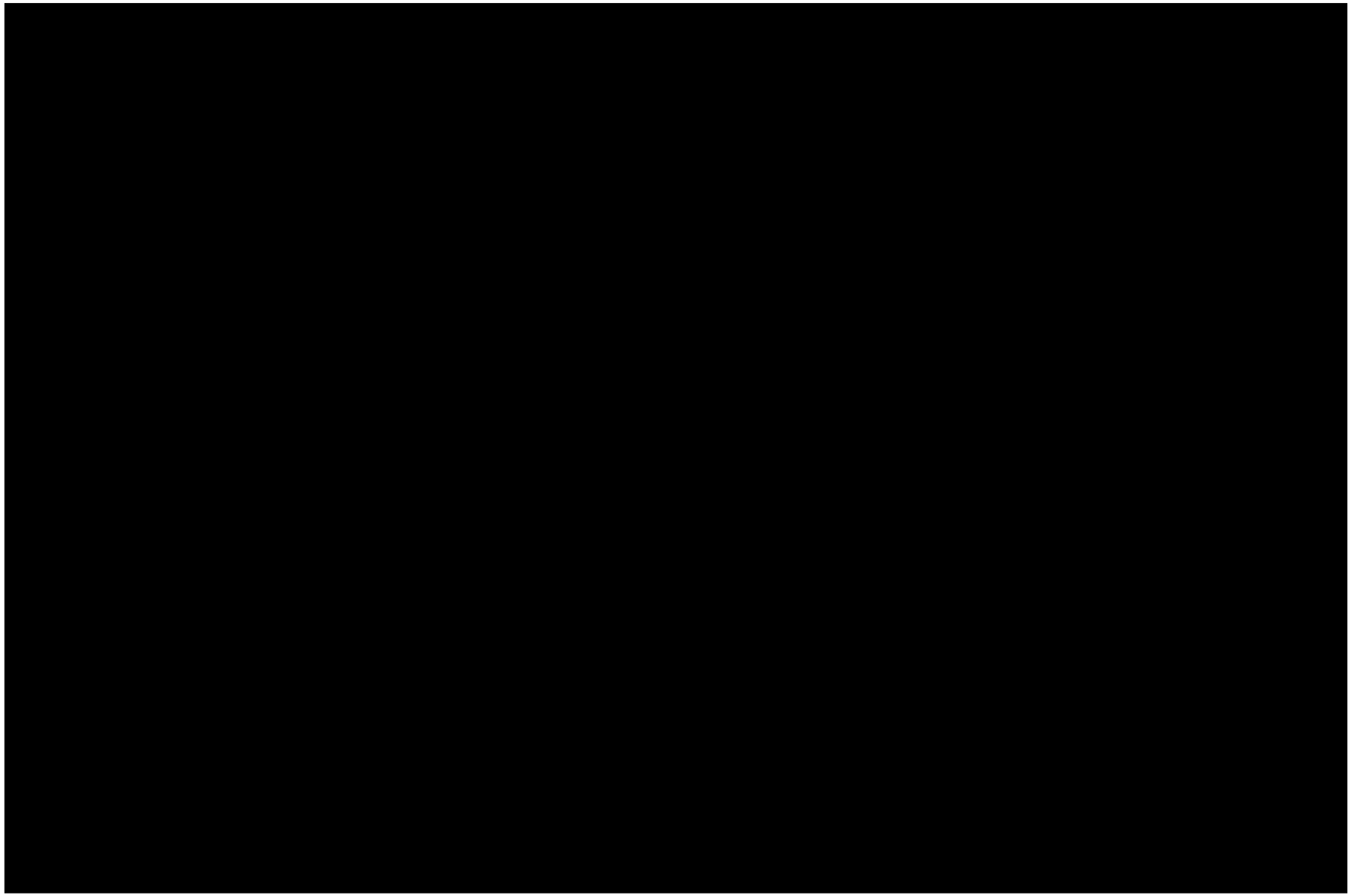


Figure 4 Visual inspection of EFS hazards and survival curves from top non-proportional-hazard candidate models (based on goodness-of-fit statistics) (full network of evidence)

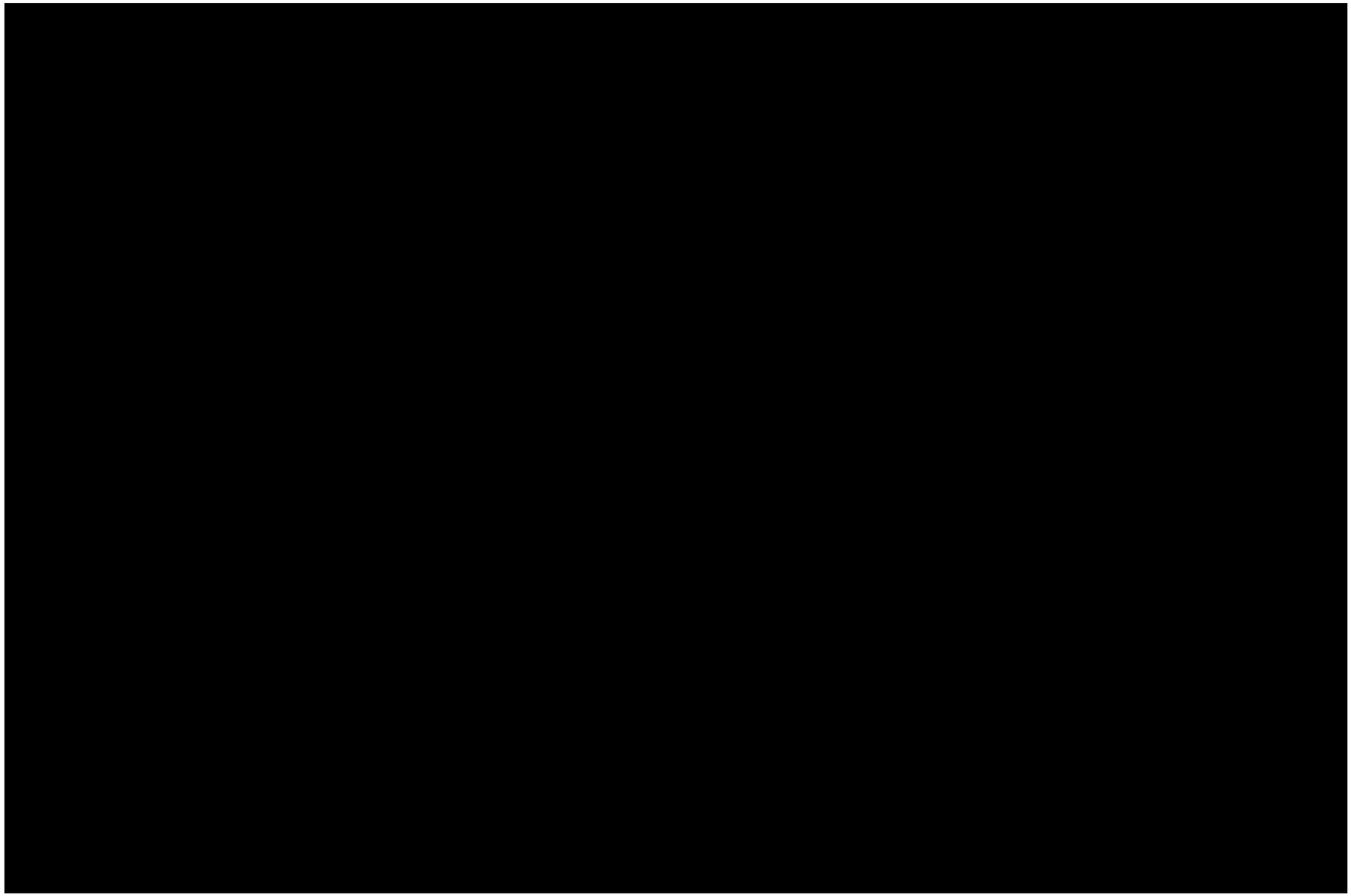


*Figure 5 Visual assessment of the base case EFS ML-NMR 4-knot M-spline model fit to each Kaplan-Meier curve in the original submitted model (CM77T, NADIM II, KN671), modeled for target populations specific to each trial**

**Note: the location of the knots is percentile-based; for PH models, these knot locations vary across trials. For NADIM II, the boundary knot is shown but for KN671 and CM77T, it is [redacted] and therefore not displayed.*

*Figure 6 Visual assessment of the base case EFS ML-NMR 4-knot M-spline modelled hazards in the original submitted model (CM77T, NADIM II, KN671), modelled for target populations specific to each trial**

**Note: the location of the knots is percentile-based; for PH models, these knot locations vary across trials. For NADIM II, the boundary knot is shown but for KN671 and CM77T, it is [redacted] and therefore not displayed.*

Overall survival (OS)

The figures that follow depict the modelled baseline hazards and survival curves from the selected model as well as the other models that had been candidates based on goodness-of-fit statistics. First, the IPD-based assessments of knot placement are provided, from which the 1-knot and 4-knot models were preferred. The 1-knot model was positioned around the [redacted], and the visual inspections did not reveal the 4-knot model to provide additional benefit; however, it was also retained as a candidate in the full network of evidence in case it was relevant for specific trials (**Figure 7** for proportional hazards models, and **Figure 8** for non-proportional hazards models). The other models for which the difference in expected log predictive density was within one standard of the top model were all non-proportional hazards models, with a greater number of knots and hence were not pursued.

Next, the visualizations of the 1-knot M-Spline model compared with other top-fitting parametric forms (4-knot M-Spline and lognormal) are provided in **Figure 9** and **Figure 10**. The visual inspection of these hazard plots showed no clear benefit of the 4-knot over the 1-knot and the lognormal functional form led to constraints that were not evident in the 1-knot M-Spline model, further supporting the choice of the flexible parametric 1-knot M-Spline model.

In **Figure 11** and **Figure 12**, the Kaplan-Meier curves from each trial are overlaid against the modelled output from the ML-NMR specific to the target population of each trial. Note that the modelled output of periNIVO+neoCT represents the meta-analysed estimate using both the CM77T and NADIM II evidence, which is more heavily weighted by the CM77T evidence base; thus, some degree of deviation between the NADIM II Kaplan-Meier curves and modelled outputs is reasonable.

Note that empirical baseline hazards are best depicted using a smoothing algorithm; hence the hazard plots were simply interpreted alongside the survival curves with Kaplan-Meier curve overlays.

Figure 7 Visual inspection of OS hazards and survival curves from proportional-hazard M-Spline-based models having different number of knots

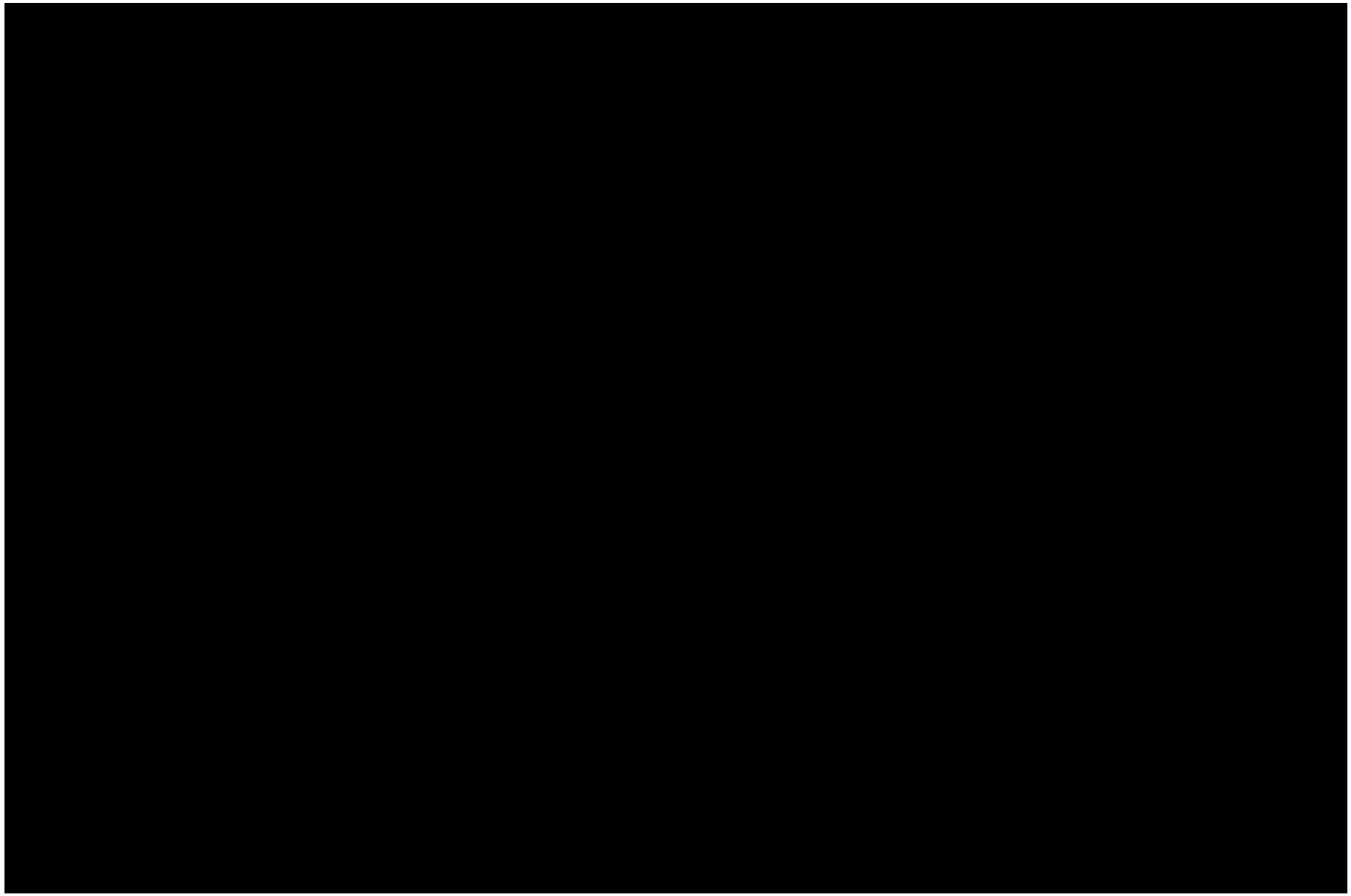


Figure 8 Visual inspection of OS hazards and survival curves from non-proportional-hazard M-Spline-based models having different number of knots

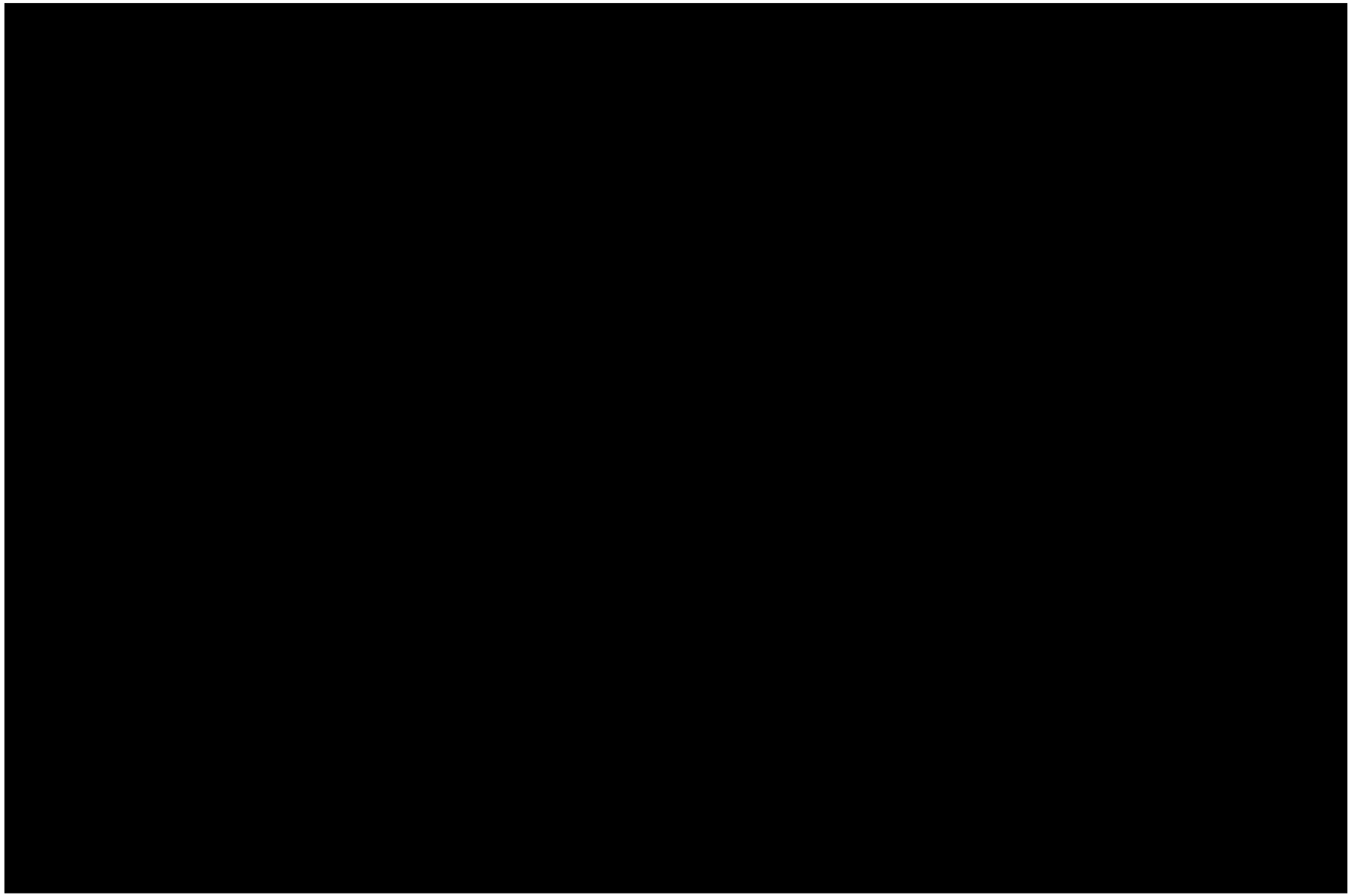


Figure 9 Visual inspection of OS hazards and survival curves from top proportional-hazard candidate models (based on goodness-of-fit statistics) (full network of evidence)

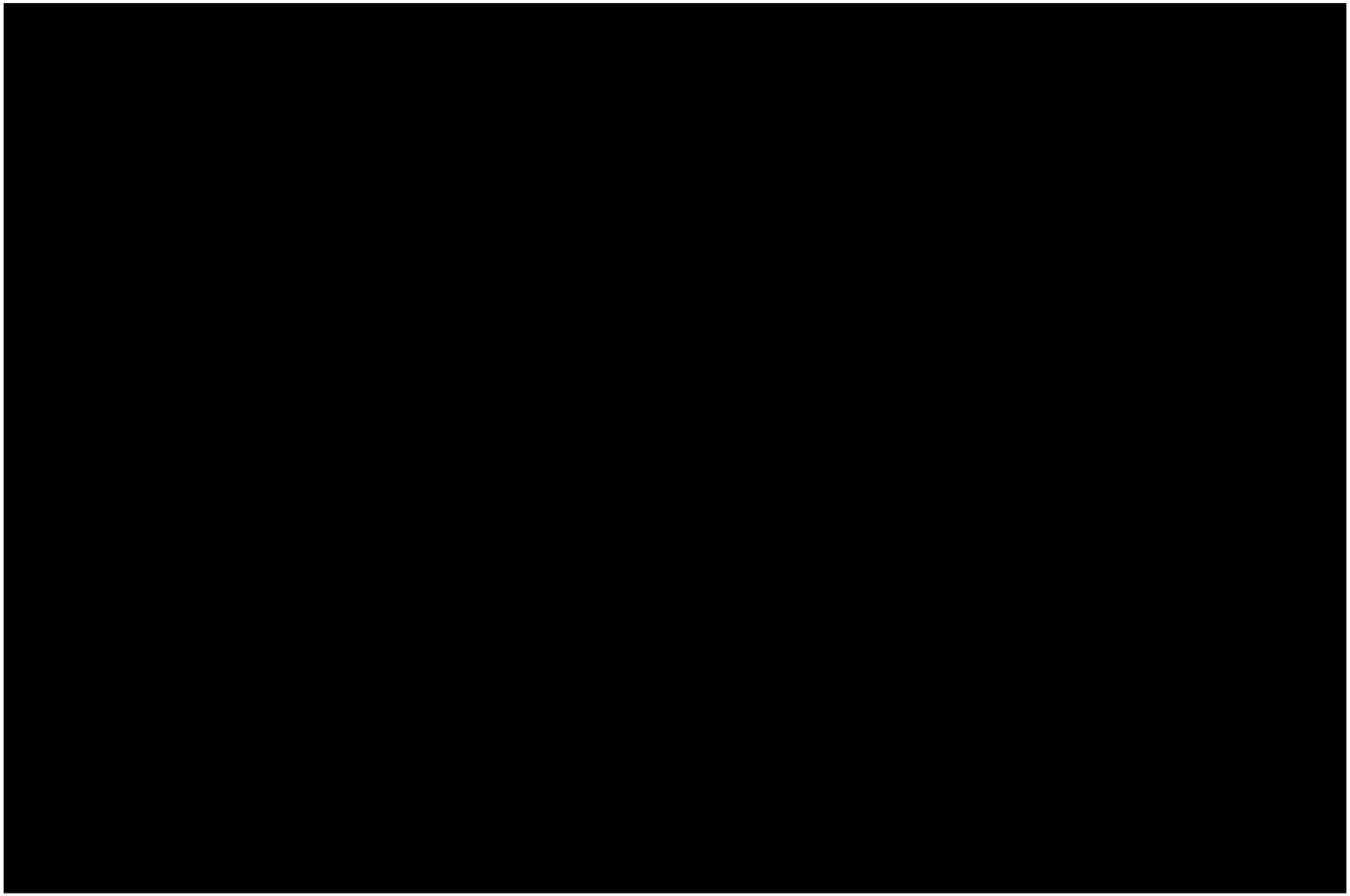
c) 

Figure 10 Visual inspection of OS hazards and survival curves from top non-proportional-hazard candidate models (based on goodness-of-fit statistics) (full network of evidence)

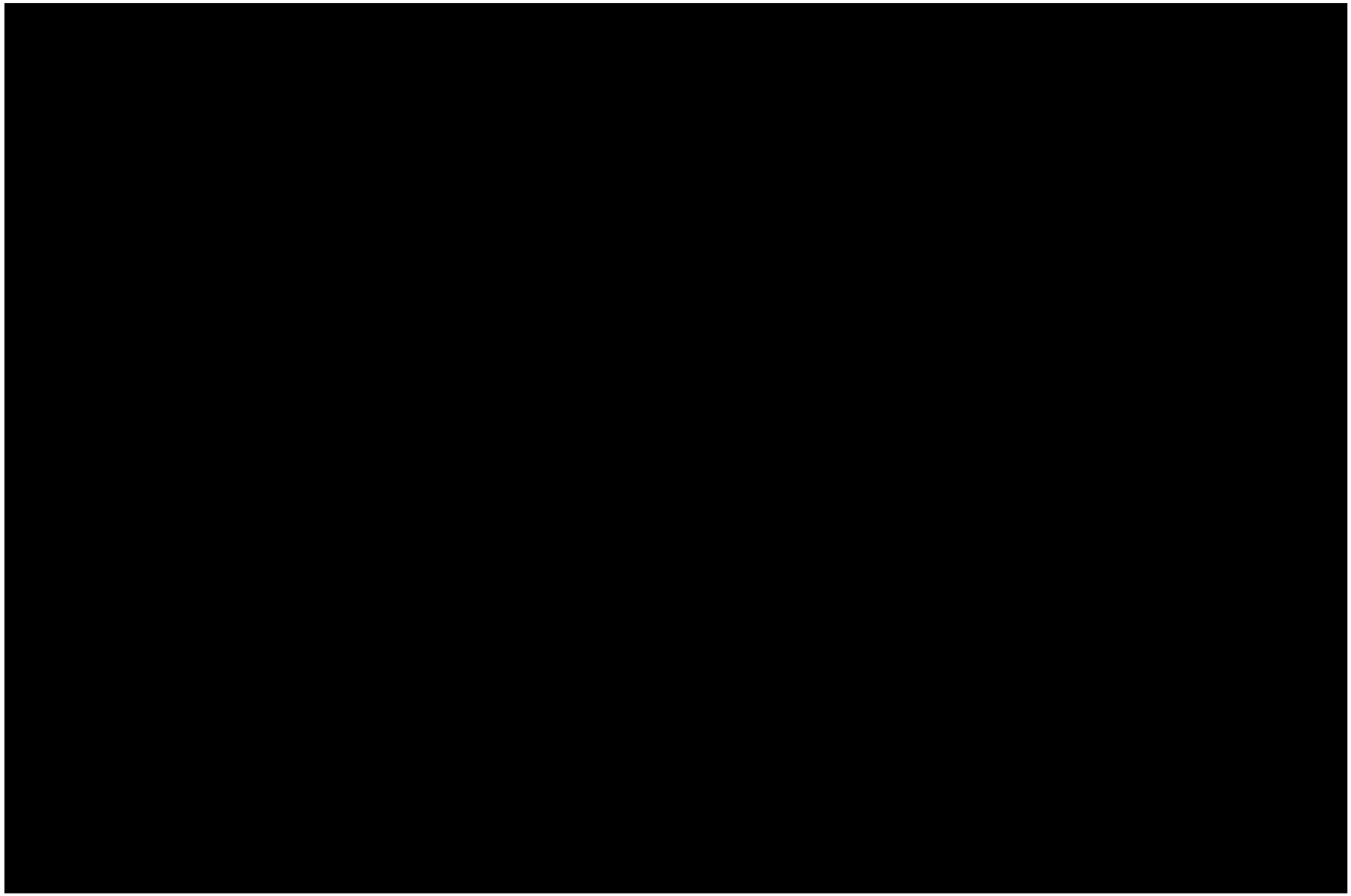


*Figure 11 Visual assessment of the base case OS ML-NMR model (1-knot M-Spline proportional hazards) fit to each Kaplan-Meier curve in the original submitted model (CM77T, NADIM II, KN671), modelled for target populations specific to each trial**

*Note: the location of the knots is percentile-based; for PH models, these knot locations vary across trials. For NADIM II, the boundary knot is shown but for KN671 and CM77T, it is [redacted] and therefore not displayed.

*Figure 12 Visual assessment of the base case OS ML-NMR (1-knot M-Spline proportional hazards) modelled hazards in the original submitted model (CM77T, NADIM II, KN671), modeled for target populations specific to each trial**

**Note: the location of the knots are percentile-based; for PH models, these knot locations vary across trials. For NADIM II, the boundary knot is shown but for KN671 and CM77T, it is [redacted] and therefore not displayed.*

Response to Question A2b):

The model fit statistics from the **Bayesian NMA** were provided in the submission in Table 10, Table 18, and Table 25. The Brooks–Gelman–Rubin (BGR) diagnostic plots and Trace Plots are presented below:

- EFS: BGR plots (**Figure 15**) and Trace plots (**Figure 16**)
- Overall-survival: BGR plots (**Figure 17**) and Trace plots (**Figure 16**)
- Pathological complete response: BGR plots (**Figure 17**) and Trace plots (**Figure 18**).

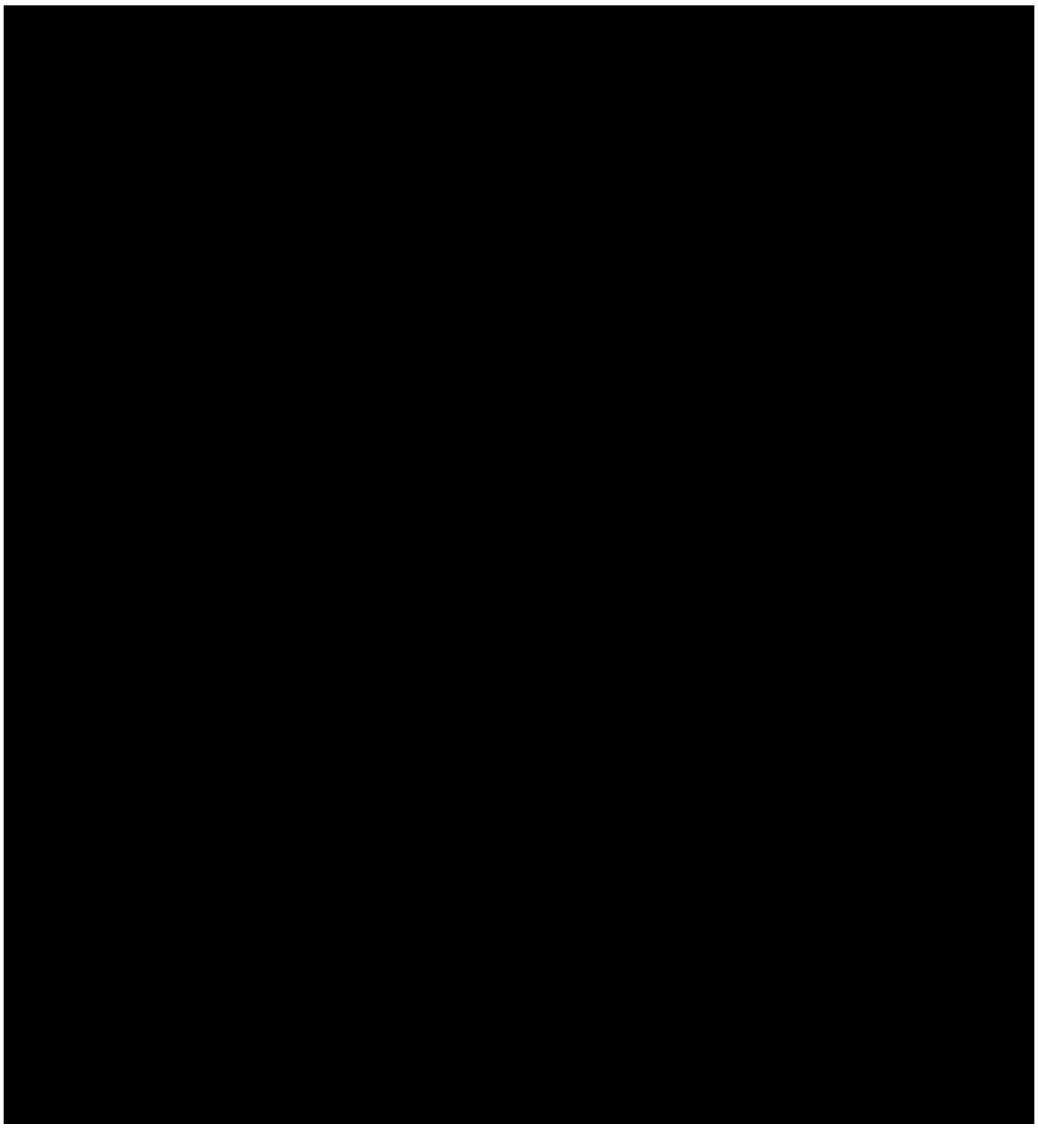
For the **FP-NMA**, the relevant deviance information criterion (DIC) plots are presented (**Figure 19, Figure 20**). It is important to note that model selection depends not only on model fit, but also on meeting the predefined heuristic described in the original NICE submission report, **Appendix Section 9**.

The BGR and trace plots are available below for the FP-NMA (which was presented in the submission from the full network of evidence):

- EFS: BGR plots (**Figure 21**) and Trace plots (**Figure 22**)
- Overall-survival: BGR plots (**Figure 23**) and Trace plots (**Figure 24**)

For the ML-NMR analyses, an external folder entitled "*ML-NMR convergence diagnostics*" contains all relevant materials on model fit and convergence. For each model (the 3-node network from the original submission and the 4-node network used in response to the current questions), three outputs are provided: coefficient summaries, trace plots, and code run warnings.

Figure 13 BGR diagnostic plots for EFS



***Note**: All plots show the shrink factor dropping quickly to ≈1.0 and staying flat indicating good convergence*

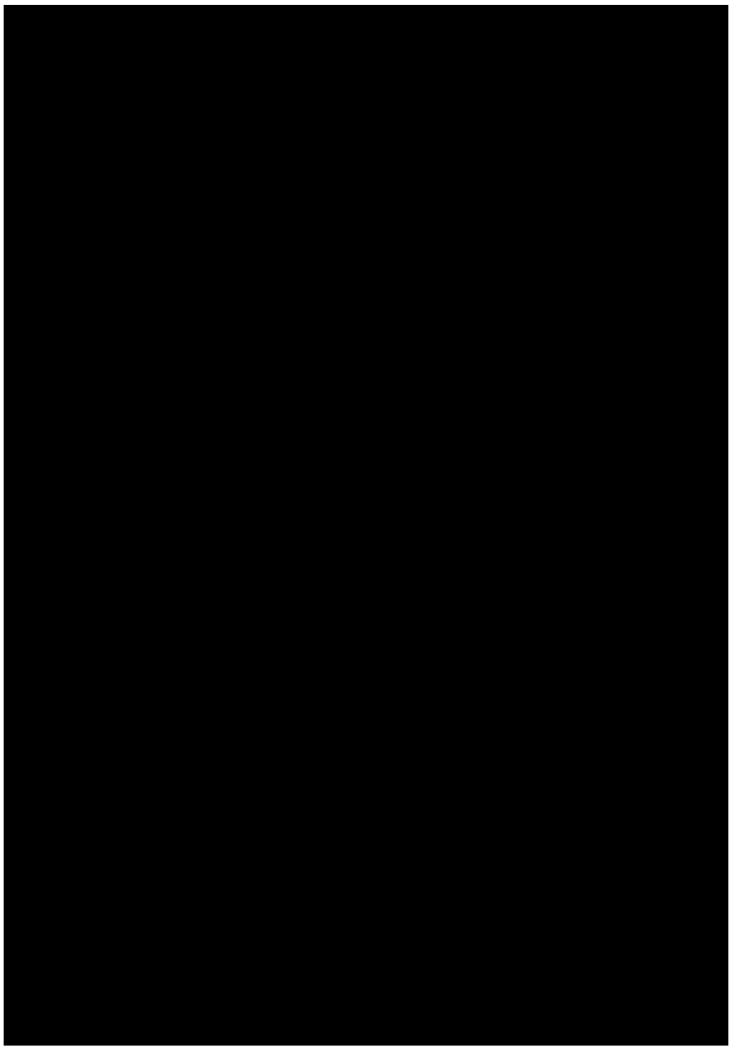
Figure 14 Trace plot of the parameter across the MCMC chains for EFS

***Note**: The overlapping, stable trajectories indicate good mixing and convergence to the target posterior distribution*

Figure 15 BGR diagnostic plots for OS

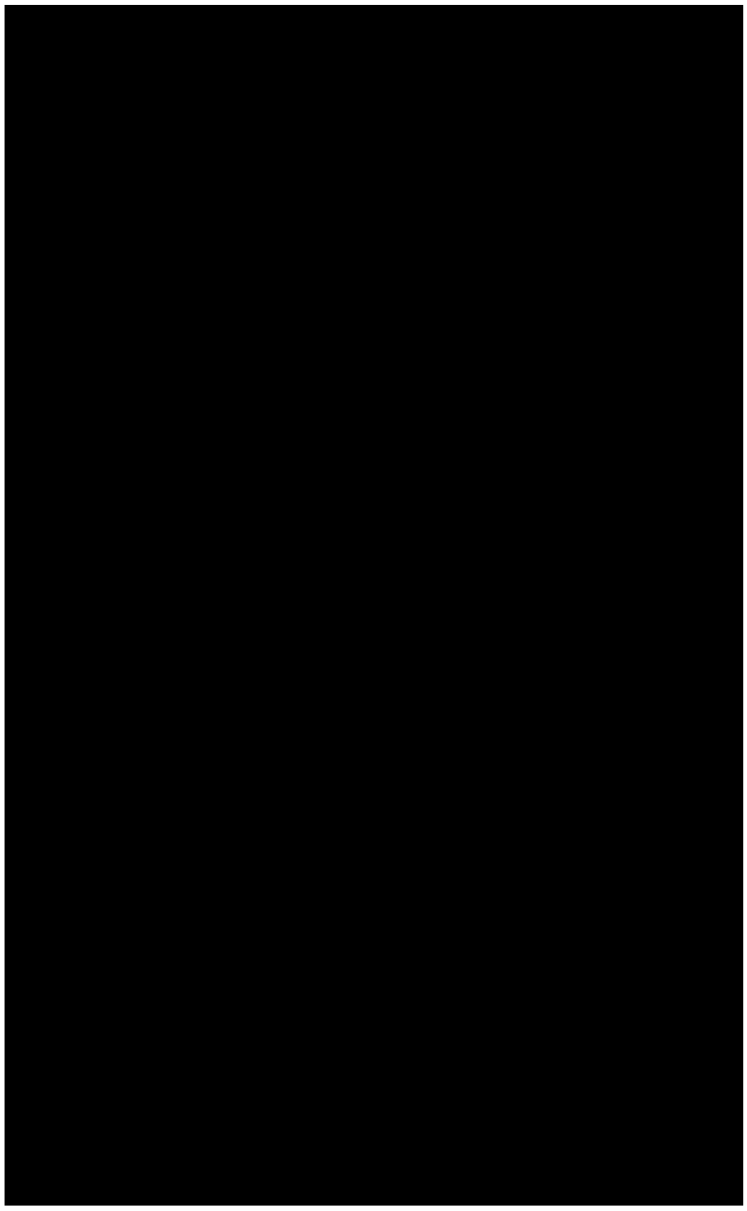
***Note**: All plots show the shrink factor dropping quickly to ≈1.0 and staying flat indicating good convergence*

Figure 16 Trace plot of the parameter across the MCMC chains for OS



***Note**: The overlapping, stable trajectories indicate good mixing and convergence to the target posterior distribution*

Figure 17 BGR diagnostic plots for pathological complete response



***Note**: All plots show the shrink factor dropping quickly to ≈1.0 and staying flat indicating good convergence*

Figure 18 Trace plot of the parameter across the MCMC chains for pathological complete response

***Note**: The overlapping, stable trajectories indicate good mixing and convergence to the target posterior distribution*

Figure 19 Standardized DICs across evaluated models for EFS and identification of candidate models based on DIC

***1o PH model:** A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d0), but no shape parameters, resulting in a proportional hazards model;**1o NPH model:** A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d0), and the shape (i.e., time-related) parameter (d1); in this model, hazard ratios could vary over time; **2o PH model:** A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d0) but no shape parameters, resulting in a proportional hazards model;**2o NPH model:** A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d0) and one shape parameter (either d1 or d2); in this model, hazard ratios could vary over time; **2o NPH model (two shape)**: A second-order fractional polynomial in which treatment effects are placed on the scale parameter (d0) and both shape parameters, d1 and d2 (these are the highest complexity models that can be fit, and they tend to overfit the data, particularly on the tails of the survival curves, so these models were not considered suitable candidate models).*
***Abbreviations:** DIC, deviance information criterion; EFS, event-free survival.*

Figure 20 Standardized DICs across evaluated models for OS and identification of candidate models based on DIC

1o PH model: *A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d0), but no shape parameters, resulting in a proportional hazards model;****1o NPH model:*** *A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d0), and the shape (i.e., time-related) parameter (d1); in this model, hazard ratios could vary over time;* ***2o PH model:*** *A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d0) but no shape parameters, resulting in a proportional hazards model;****2o NPH model:*** *A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d0) and one shape parameter (either d1 or d2); in this model, hazard ratios could vary over time;* ***2o NPH model (two shape)****: A second-order fractional polynomial in which treatment effects are placed on the scale parameter (d0) and both shape parameters, d1 and d2 (these are the highest complexity models that can be fit, and they tend to overfit the data, particularly on the tails of the survival curves, so these models were not considered suitable candidate models).*

Abbreviations: *DIC, deviance information criterion; OS, overall survival*

Figure 21 BGR diagnostic plots for EFS from the fractional polynomial NMA in the CM77T, KN671, NADIM II network

***Note**: All plots show the shrink factor dropping quickly to ≈1.0 and staying flat indicating good convergence*

Figure 22 Trace plot of the parameter across the MCMC chains for EFS in the CM77T, KN671, NADIM II network

***Note**: The overlapping, stable trajectories indicate good mixing and convergence to the target posterior distribution*

Figure 23 BGR diagnostic plots for OS from the fractional polynomial NMA in the CM77T, KN671, NADIM II network

***Note**: All plots show the shrink factor dropping quickly to ≈1.0 and staying flat indicating good convergence*

Figure 24 Trace plot of the parameter across the MCMC chains for OS in the CM77T, KN671, NADIM II network

***Note**: The overlapping, stable trajectories indicate good mixing and convergence to the target posterior distribution*

A3. Priority question. Please conduct indirect treatment comparisons to compare nivolumab with pembrolizumab, and nivolumab with durvalumab using only data from CheckMate-77T (i.e., excluding the NADIM-II study), KEYNOTE-671 and the AEGEAN trial. Please conduct ITCs using the traditional Bayesian network meta-analysis (NMA), and ML-NMR methods reported in the company submission.

a) **With regards to the ML-NMR, please re-evaluate the available data on prognostic and treatment effect modifiers and adjust for those deemed significant (e.g. those recommended by the company's clinical experts).**
b) **With regards to the ITCs conducted, please provide results for a fixed effects model as well as a random effects model.**

If the company is unable to include the AEGEAN trial in their analyses, please conduct the requested ITCs including only CheckMate-77T and KEYNOTE-671, to enable a comparison of nivolumab versus pembrolizumab.

For each of the ITCs conducted, please provide:

a) **results for:**
    i) **EFS using the most consistent outcome data from each trial <u>as the EAG is concerned that the current analyses mix blinded independent central review (BICR)-assessed EFS and investigator-assessed EFS data.</u> If sufficient data are available, please conduct separate analyses for:**
        1) **investigator-assessed EFS; and**
        2) **blinded independent central review (BICR)-assessed EFS.**
    ii) **Overall survival;**
    iii) **Time-to-treatment discontinuation.**

b) **details of the methods used (including convergence plots and model fit statistics) along with working code and data files.**

Response to Question A3 a.i:

Exploration of inconsistency in outcome definition across trials (BICR vs investigator)

We acknowledge the EAG's concern regarding the mixing of blinded independent central review (BICR)- and investigator-assessed outcomes. The inconsistency was influenced by data availability from KN671, which focused on EFS per investigator, while AEGEAN focused on EFS per BICR. However, EFS per BICR from KN671 and per investigator from AEGEAN were identified from their EPARs, but from earlier data cuts (**Table 1**). As a result, it was not possible to conduct analyses using a uniform assessor at the most recent data cut-off from all trials.

Table 1 EFS data available across trails in the subnetwork

Trial	Database lock	Source	Assessor	Used in		
				Bayesian NMA	Bucher ITC (BICR)	Bucher ITC (Investigator)
AEGEAN	May 10, 2024	Heymach WCLC 2024	BICR	✓	✓	×
	Nov 10, 2022	Imfinzi EPAR (Feb 27, 2025)	BICR	×	✓	×
			Investigator	×	×	✓
KN671	Aug 19, 2024	Majem ESMO 2024	Investigator	✓	×	✓
	Jul 10, 2023	Spicer Lancet 2024	Investigator	×	×	×
	Jul 29, 2022	Wakelee NEJM 2023	Investigator	×	×	✓
		Keytruda EPAR; (Feb 22, 2024)	BICR	×	✓	×
CM77T	Dec 16, 2024	Data on file	BICR	✓	✓	×
			Investigator	×	×	✓

Abbreviations: *BICR, blinded independent central review; CheckMate 77T, CM77T; EFS, event-free survival; ITC, indirect treatment comparison; KN671, KeyNote 671; NMA, network meta-analysis.*

To address the EAG's concern, we conducted Bucher ITCs for EFS using consistent outcome assessors (BICR or investigator) in line with the request (**Table 2**). For each comparison, we performed ITCs using: (1) the most recent data available, and (2) earlier data cuts where both BICR- and investigator-assessed EFS were available at the same cut-off, to explore differences in generated estimates of relative effect by assessment method. In CM77T, EFS per BICR and per investigator were closely aligned; a similar pattern, but with slightly more variation, was observed in AEGEAN. As a result, outcome definition had minimal impact on the estimated effect for the comparison between periNIVO+neoCT and periDURVA+neoCT. In contrast, EFS by investigator in KN671 was notably lower than that by BICR. This difference affected the direction of the estimated effect for the comparison between periNIVO+neoCT and periPEMBRO+neoCT, which favored periNIVO+neoCT when BICR was used consistently. However, the point estimate remained close to the null. Overall, these findings suggest that the mixing of BICR- and investigator-assessed EFS in our analyses is unlikely to have materially impacted the conclusions.

Table 2 Bucher ITC output: periNIVO+neoCT vs comparators for EFS

	Data input: *vs* neoCT HR (95% Cr)	**Database lock date**	**Results of Bucher ITC: periNIVO+neoCT *vs*** HR (95% CI)
Investigator assessed Bucher ITC (using latest available data cut)			
periNIVO+neoCT	[redacted]	[redacted]	[redacted]
periPEMBRO+neoCT	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
periDURVA+neoCT	[redacted]	[redacted]	[redacted]
Blinded independent central review			

	Data input: *vs* neoCT HR (95% Cr)	Database lock date	Results of Bucher ITC: periNIVO+neoCT *vs* HR (95% CI)
periNIVO+neoCT	[redacted]	[redacted]	[redacted]
periPEMBRO+neoCT	[redacted]	[redacted]	[redacted]
periDURVA+neoCT	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

**Unstratified hazard ratio*
***Digitized from forest plot*
Abbreviations: *CI, confidence interval; EFS, event-free survival; HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Peri-operative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Peri-operative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Peri-operative pembrolizumab-neoadjuvant chemotherapy*

Response to Question A3 Standard Bayesian NMA

We conducted the requested Bayesian NMA using a restricted subnetwork including CM77T, KN671, and AEGEAN, and excluding NADIM II. For reasons previously described, the Bayesian NMA was conducted using the most recent evidence available for each trial, regardless of assessor.

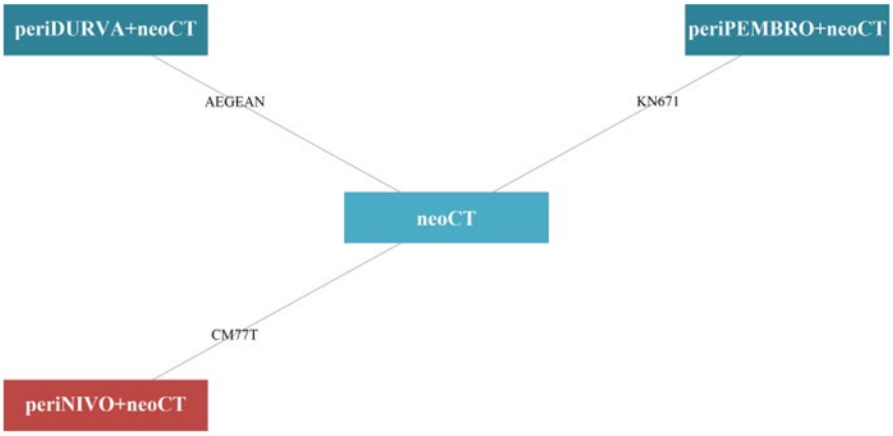
For **EFS**, relevant results are provided below

- Network diagram (**Figure 25**)
- Model fit statistics (**Table 3**)
    - Note: As described in in the original NICE submission report **Section 5.2.1.1**, while the random effects model was selected *a priori*, the sparse evidence base informing the EFS network on any given network connection (at most 3 RCTs) provided insufficient evidence for precisely calculating the between-study standard deviation, which was estimated from a prior distribution informed as a uniform distribution ranging from [redacted]. The informed priors were defined based on the posterior of the between study standard deviation obtained from a vague prior from the largest available network across all base case and sensitivity analyses conducted. As a result, in the submitted report we focused on fixed effect model results, but also contrasted fixed and random effects model results, for full transparency.
- Fixed effect and random effects model results *vs neoCT* (**Table 4**)
- Fixed effect results *periNIVO+neoCT vs other* (**Figure 26**)
    - The removal of NADIM II from the network of evidence led to a modest shift on the estimate of relative effect between periNIVO+neoCT and neoCT, reflective of the small weight the NADIM II trial had on the generated estimate (from [redacted] in Figure 7 of the original NICE submission report to [redacted]). In consequence, the relative estimate of effect between periNIVO+neoCT and periPEMBRO+neoCT moved away from the null, from [redacted] in Figure 8 of the original NICE submission report to [redacted], which

has no impact on the original study conclusions. The newly estimated hazard ratio (HR) between periNIVO+neoCT and periDURVA+neoCT indicates a potential EFS benefit for periNIVO+neoCT but the credible interval (CrI) crossed the null value (HR=[redacted])

- Brooks–Gelman–Rubin (BGR) diagnostic plots (**Figure 27**) and Trace Plots (**Figure 28**)

Figure 25 Network diagram for subnetwork of interest



Note: *The reference treatment is neoCT.*
Abbreviations: *EFS, event-free survival; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Peri-operative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Peri-operative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Peri-operative pembrolizumab-neoadjuvant chemotherapy.*

Table 3 Model fit statistics for standard Bayesian NMA output for EFS in the KN671, AEGEAN and CM77T network

Statistic	Random effects model	Fixed effect model
DIC (residual deviance + leverage)	[redacted]	[redacted]
sd (95% CrI)	[redacted]	[redacted]

Note: *The DIC estimate for the random effects model was -1.286, while the fixed effect model was -1.295; differences in DIC are negligible.*
Abbreviations*: CrI, credible interval; DIC, Deviance Information Criterion; EFS, event-free survival; NMA, network meta-analysis; sd, standard deviation.*

Table 4 Standard Bayesian NMA output: vs. reference treatment (neoCT) for EFS in the KN671, AEGEAN and CM77T network

Intervention (vs. neoCT)	Random effects model HR (95% CrI)	Fixed effect model HR (95% CrI)
periPEMBRO+neoCT	[redacted]	[redacted]
periNIVO+neoCT	[redacted]	[redacted]
periDURVA+neoCT	[redacted]	[redacted]
neoCT	[redacted]	[redacted]

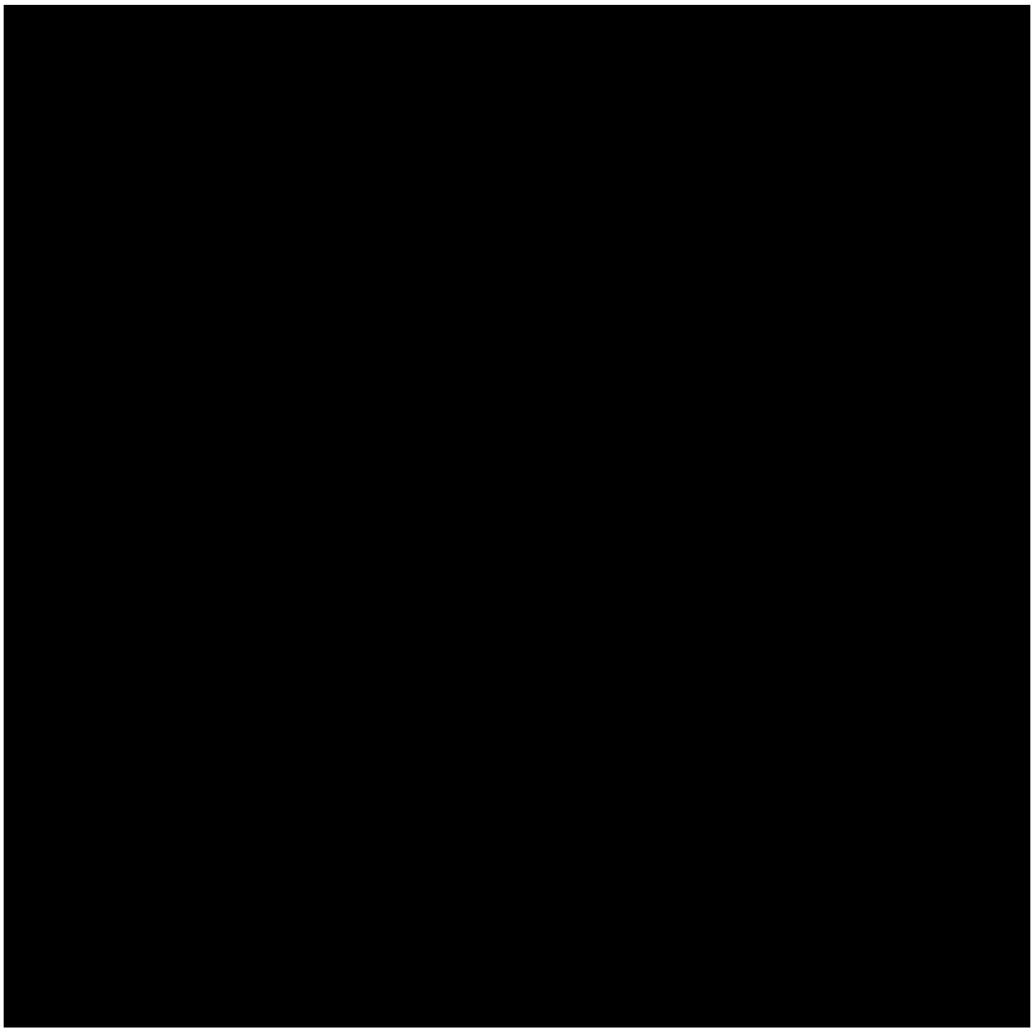
Abbreviations: *CrI, credible interval; EFS, event-free survival; HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; NMA, network meta-analysis; periDURVA+neoCT, Peri-operative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Peri-operative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Peri-operative pembrolizumab-neoadjuvant chemotherapy.*

Figure 26 Standard Bayesian NMA output: periNIVO+neoCT vs comparators for EFS in the KN671, AEGEAN and CM77T network

[redacted]

Abbreviations: *CrI, credible interval; EFS, event-free survival; HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; NMA, network meta-analysis; periNIVO+neoCT, Peri-operative nivolumab-neoadjuvant chemotherapy*

Figure 27 BGR diagnostic plots for EFS in the KN671, AEGEAN and CM77T network



Note*: All four plots (d[2], d[3], d[4], deviance) show the shrink factor dropping quickly to ≈1.0 and staying flat indicating good convergence*
Abbreviations: *EFS, event-free survival*

Figure 28 Trace plot of the parameter across the MCMC chains for EFS in the KN671, AEGEAN and CM77T network

***Note**: The overlapping, stable trajectories indicate good mixing and convergence to the target posterior distribution*
***Abbreviations:** EFS, event-free survival*

For **OS**, relevant results are provided below

- Network diagram (**Figure 25**)
- Model fit statistics (**Table 5**)
- Fixed effect and random effects model results *vs neoCT* (**Table 6**)
- Fixed effect results *periNIVO+neoCT vs other* (**Figure 29**)
    - The removal of NADIM II from the network of evidence led to a shift on the estimate of relative effect between periNIVO+neoCT and neoCT, from [redacted] in Figure 16 of the original NICE submission report to [redacted]. In consequence, the relative estimate of effect for OS between periNIVO+neoCT and periPEMBRO+neoCT moved away from the null, from [redacted] in Figure 16 of the original NICE submission report to [redacted]; the estimate was associated with large uncertainty (95% CrI: [redacted]) (**Figure 29**). The newly estimated HR between periNIVO+neoCT and periDURVA+neoCT indicates similar risk of OS between these two regimens (HR=[redacted]).
- BGR diagnostic plots (**Figure 30**) and Trace Plots (**Figure 31**)

Table 5 Model fit statistics for standard Bayesian NMA output for OS in the KN671, AEGEAN and CM77T network

Statistic	Random effects model	Fixed effect model
DIC (residual deviance + leverage)	[redacted]	[redacted]
sd (95% CrI)	[redacted]	[redacted]

***Note**: Given that the DIC was lower for fixed effect model, the fixed effect model was selected.*
***Abbreviations**: CrI, credible interval; DIC, Deviance Information Criterion; OS, overall survival; sd, standard deviation.*

Table 6 Standard Bayesian NMA output: vs. reference treatment (neoCT) for OS in the KN671, AEGEAN and CM77T network

Intervention (vs. neoCT)	Random effects model HR (95% CrI)	Fixed effect model HR (95% CrI)
periPEMBRO+neoCT	[redacted]	[redacted]
periNIVO+neoCT	[redacted]	[redacted]
periDURVA+neoCT	[redacted]	[redacted]
neoCT	[redacted]	[redacted]

***Abbreviations:** CrI, credible interval; HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; NMA, network meta-analysis; OS, overall survival; periDURVA+neoCT, Peri-operative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Peri-operative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Peri-operative pembrolizumab-neoadjuvant chemotherapy.*

Figure 29 Standard Bayesian NMA output: periNIVO+neoCT vs comparators for OS in the KN671, AEGEAN and CM77T network

***Abbreviations:** CrI, credible interval; HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; NMA, network meta-analysis; OS, overall survival; periNIVO+neoCT, Peri-operative nivolumab-neoadjuvant chemotherapy*

Figure 30 BGR diagnostic plots for OS in the KN671, AEGEAN and CM77T network

***Note**: All four plots (d[2], d[3], d[4], deviance) show the shrink factor dropping quickly to ≈1.0 and staying flat indicating good convergence*

Figure 31 Trace plot of the parameter across the MCMC chains for OS in the KN671, AEGEAN and CM77T network

***Note**: The overlapping, stable trajectories indicate good mixing and convergence to the target posterior distribution*

For **time to treatment discontinuation (TTD)**, no analysis could be conducted including KN671 or AEGEAN, as this outcome was not reported in either study.

Response to Question A3 [ML-NMR]:

Results from a revised network involving CM77T (i.e., excluding the NADIM-II study), KN671 and the AEGEAN trial (**Figure 32**) are provided below for both EFS and OS. Data on time-to-treatment discontinuation were not available in AEGEAN or KN671, and hence this analysis was not run.

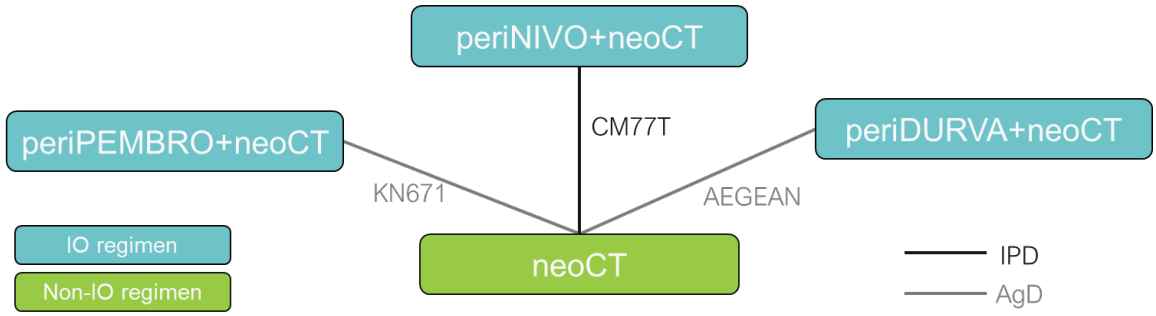
With regard to A3 sub-question 1): The initial evaluation of prognostic and effect modifying factors had been based on a comprehensive set of IO-based trials in the resectable NSCLC setting (CM816, AEGAN, NADIM II, KN671, CM77T), as reported in the original submission **Appendix 4**, as well as data on non-IOs. Assumptions regarding prognostic and effect modification remain the same when limiting the

evidence base to only the reduced set of RCTs (AEGAN, KN671, CM77T) (as can be established by reviewing the relevant plots and data points in the original submission **Appendix 4**). Thus, the adjustment factors in the analysis presented below are the same as the base case factors in the original submission (**Table 56** in original submission: stage and sex as prognostic factors, and stage and PD-L1 expression as effect modifying factors).

With regard to A3 sub-question 2): Random effects ML-NMR models were not fit. The ML-NMR was intended to explain potential between-studies heterogeneity through adjustment; as such, it is anticipated that any residual heterogeneity would be very small. Furthermore, there was only one trial per network connection meaning that the between-studies variance would have to be based on informed priors; attempts to run random effects models resulted in extremely long run times (>18 hours per model); it was not feasible to provide empirical results.

With regard to A3 sub-question a) i): EFS per investigator was not available as Kaplan-Meier data from AEGEAN, hence the ML-NMR was not re-run using a common definition; however, Bucher ITCs were performed to assess the sensitivity of findings on the method of EFS assessment (**Table 2**).

Figure 32 Network diagram for EFS and OS ML-NMR



***Abbreviations**: AgD, aggregate-level data; EFS, event-free survival; IPD, individual patient-level data; IO, immunotherapy; neoCT, Neoadjuvant chemotherapy; OS, overall survival; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*

EFS

Marginal estimates of EFS survival – predicted for the target population that aligns with CM77T patient population – are presented in **Figure 33**, based on the 4-knot spline PH model.

At all times, the predicted survival rates were similar between periNIVO+neoCT and periPEMBRO+neoCT (**Figure 33**; **Table 7**). The estimated HRs for this comparison were [redacted] time (HR, [redacted] 95% CrI, [redacted]; **Figure 34**; **Table 8**; **Table 9**). For the comparison between periNIVO+neoCT and periDURVA+neoCT, the

estimated HR was [redacted] (HR, [redacted]; 95% CrI, [redacted]) (**Figure 34**; **Table 8**; **Table 9**)

Convergence plots are provided in the external folder provided entitled "*ML-NMR convergence diagnostics > EFS 4 node model*" ; and visual assessments of fit between the Kaplan-Meier and modeled data from the current ML-NMR model (based on target populations corresponding to each trial) are provided in **Figure 35**; further details regarding model fit statistics and visual assessments are provided in the response to question **A2**.

*Figure 33 CM77T population-adjusted survival curves for the 4-knot spline proportional hazards ML-NMR model**

***Abbreviations**: EFS, event-free survival; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*

**Knot locations are denoted by vertical dashed lines; knots were placed at [redacted] months based on quantiles of EFS event locations.*

Table 7 CM77T population-adjusted EFS survival estimates from the 4-knot M-spline proportional hazards ML-NMR model

Regimen	% EFS S(t) 6 months	1 year	2 years	3 years	4 years	5 years
periNIVO+neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periPEMBRO+neoCT						
periDURVA+neoCT						
neoCT						

Abbreviations: *EFS, event-free survival; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*

*Figure 34 CM77T population-adjusted curves of hazard ratios from the 4-knot M-spline proportional hazards ML-NMR model**

periNIVO+neoCT vs. each comparator

Each comparator vs. neoCT (reference treatment)

***Abbreviations**: HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*
**Knot locations are denoted by vertical dashed lines; knots were placed at 3.4, 6.9, 10.5, and 18.7 months based on quantiles of EFS event locations.*

*Table 8 CM77T population-adjusted hazard ratios from the 4-knot M-spline proportional hazards ML-NMR model at 12 months**

Treatment A	Treatment B	EFS HR at 12 months* (95% CrI)
periNIVO+neoCT vs. comparators		
periNIVO+neoCT	periPEMBRO+neoCT	[redacted]
periNIVO+neoCT	periDURVA+neoCT	[redacted]
periNIVO+neoCT	neoCT	[redacted]
Comparators vs. neoCT		
periNIVO+neoCT	neoCT	[redacted]
periPEMBRO+neoCT	neoCT	[redacted]
periDURVA+neoCT	neoCT	[redacted]

***Abbreviations**: CrI, credible interval; EFS, event-free survival; HR, hazard ratio; ML-NMR, multilevel network meta-regression; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*

As annotated by Phillippo et al. 2024, population-average marginal hazard ratios mathematically must vary over time in the presence of covariates, even when using model structures that are conventionally considered to be proportional hazard models. However, as shown in **Figure 34, these changes are minimal over time and hence a representative estimate at 12 months is presented for simplicity.*

Table 9 CM77T population-adjusted hazard ratios from the 4-knot M-spline proportional hazards ML-NMR model at all times

Treatment A	Treatment B	EFS HR at 6 months* (95% CrI)	EFS HR at 12 months* (95% CrI)	EFS HR at 18 months* (95% CrI)	EFS HR at 24 months* (95% CrI)	EFS HR at 30 months* (95% CrI)	EFS HR at 36 months* (95% CrI)	EFS HR at 42 months* (95% CrI)	EFS HR at 48 months* (95% CrI)	EFS HR at 54 months* (95% CrI)	EFS HR at 60 months* (95% CrI)
periNIVO+neoCT vs. comparators											
periNIVO+neoCT	periPEMBRO+neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periNIVO+neoCT	periDURVA+neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periNIVO+neoCT	neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparators vs. neoCT											
periNIVO+neoCT	neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periPEMBRO+neoCT	neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periDURVA+neoCT	neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: CrI, credible interval; EFS, event-free survival; HR, hazard ratio; ML-NMR, multilevel network meta-regression; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*

As annotated by Phillippo et al. 2024, population-average marginal hazard ratios mathematically must vary over time in the presence of covariates, even when using model structures that are conventionally considered to be proportional hazard models. However, as shown in **Figure 34, these changes are minimal over time and hence a representative estimate at 12 months is presented for simplicity.*

*Figure 35 Visual assessment of the base case EFS ML-NMR model fit to each Kaplan-Meier curve, modeled for target populations specific to each trial**

***Abbreviations**: EFS, event-free survival; ML-NMR, multilevel network meta-regression; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*

**Knots are specified differently for each target trial, based on percentiles.*

OS

Marginal estimates of OS survival – predicted for the target population that aligns with CM77T patient population – are presented in **Figure 36**, based on the 1-knot spline PH model.

At all times, the predicted survival rates were [redacted] periNIVO+neoCT and periPEMBRO+neoCT (**Figure 36; Table 10**). The estimated HRs for this comparison were [redacted] (HR=[redacted]; CrI: [redacted]; **Figure 37; Table 11** and **Table 12**). For the comparison between periNIVO+neoCT and periDURVA+neoCT, the estimated HR [redacted] but the 95% CrIs [redacted] (HR, [redacted]; 95% CrI, [redacted]) (**Figure 37; Table 11**; **Table 12**)

Convergence plots are provided in the external folder provided entitled "*ML-NMR convergence diagnostics > EFS 4 node model*" ; and visual assessments of fit between the Kaplan-Meier and modelled data from the current ML-NMR model (based on target populations corresponding to each trial) are provided in **Figure 38**; further details regarding model fit statistics and visual assessments are provided in the response to question **A2**.

*Figure 36 CM77T population-adjusted survival curves for the 1-knot spline proportional hazards ML-NMR model**

***Abbreviations**: ML-NMR, multilevel network meta-regression; neoCT, Neoadjuvant chemotherapy; OS, overall survival; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*
** Knot locations are denoted by vertical dashed lines; knots were placed at [redacted] months based on quantiles of OS event locations.*

Table 10 CM77T population-adjusted OS survival estimates from the 1-knot M-spline proportional hazards ML-NMR model

	% OS S(t)					
Regimen	**6 months**	**1 year**	**2 years**	**3 years**	**4 years**	**5 years**
periNIVO+neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periPEMBRO+neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periDURVA+neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: ML-NMR, multilevel network meta-regression; OS, overall survival; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*

*Figure 37 CM77T population-adjusted curves of hazard ratios from the 1-knot M-spline proportional hazards ML-NMR model**

periNIVO+neoCT vs. each comparator

Each comparator vs. neoCT (reference treatment)

***Abbreviations**: HR, hazard ratio; ML-NMR, multilevel network meta-regression; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*
** Knot locations are denoted by vertical dashed lines; knots were placed at [redacted] months based on quantiles of OS event locations.*

Table 11 CM77T population-adjusted hazard ratios from the 1-knot M-spline proportional hazards ML-NMR model at 12 months

Treatment A	Treatment B	OS HR at 12 months* (95% CrI)
periNIVO+neoCT vs. comparators		
periNIVO+neoCT	periPEMBRO+neoCT	[redacted]
periNIVO+neoCT	periDURVA+neoCT	[redacted]
periNIVO+neoCT	neoCT	[redacted]
Comparators vs. neoCT		
periNIVO+neoCT	neoCT	[redacted]
periPEMBRO+neoCT	neoCT	[redacted]
periDURVA+neoCT	neoCT	[redacted]

***Abbreviations**: CrI, credible interval; ML-NMR, multilevel network meta-regression; OS,overall survival; HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*

As annotated by Phillippo et al. 2024, population-average marginal hazard ratios mathematically must vary over time in the presence of covariates, even when using model structures that are conventionally considered to be proportional hazard models. However, as shown in **Figure 34, these changes are minimal over time and hence a representative estimate at 12 months is presented for simplicity.*

Table 12 CM77T population-adjusted hazard ratios from the 1-knot M-spline proportional hazards ML-NMR model at all times

Treatment A	Treatment B	OS HR at 6 months* (95% CrI)	OS HR at 12 months* (95% CrI)	OS HR at 18 months* (95% CrI)	OS HR at 24 months* (95% CrI)	OS HR at 30 months* (95% CrI)	OS HR at 36 months* (95% CrI)	OS HR at 42 months* (95% CrI)	OS HR at 48 months* (95% CrI)	OS HR at 54 months* (95% CrI)	OS HR at 60 months* (95% CrI)
periNIVO+neoCT vs. comparators											
periNIVO+neoCT	periPEMBRO+neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periNIVO+neoCT	periDURVA+neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periNIVO+neoCT	neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparators vs. neoCT											
periNIVO+neoCT	neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periPEMBRO+neoCT	neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
periDURVA+neoCT	neoCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *CrI, credible interval; HR, hazard ratio; ML-NMR, multilevel network meta-regression; OS, overall survival*

*Figure 38 Visual assessment of the base case OS ML-NMR model fit to each Kaplan-Meier curve, modeled for target populations specific to each trial**

***Abbreviations**: neoCT, Neoadjuvant chemotherapy; ML-NMR, multilevel network meta-regression; OS, Overall survival; periDURVA+neoCT, Perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, Perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Perioperative pembrolizumab-neoadjuvant chemotherapy.*

**Knots are specified differently for each target trial, based on percentiles.*

A4. Priority question. As a scenario analysis for the ML-NMR requested in question A3, please adjust for all potential prognostic and treatment effect modifiers and all available baseline characteristics (i.e. conduct fully adjusted analyses).

A model adjusting for all potential prognostic and treatment effect modifiers was provided as a sensitivity analysis in the original NICE submission report (**Table 76**); however, as noted in that report, sensitivity analyses were run using the broader evidence base.

The "Covariate inclusion (full)" sensitivity analysis model has now been run on the network requested in question A3 (i.e., AEGEAN, KN671, CM77T), and results are compared side-by-side with the base case model results (also provided in question A3), for periNIVO+neoCT vs. periPEMBRO+neoCT (**Table 13**), periNIVO+neoCT vs. periDURVA+neoCT (**Table 14**) and periNIVO+neoCT vs. neoCT (**Table 15**).

The factors included in the model are defined in the original submission **Table 56** and includes all key baseline characteristics reported across trials. Prognostic factors were: disease stage, ECOG performance status, sex, region, smoking status, histology, and PD-L1 expression level; treatment effect modifiers were: PD-L1 expression level, disease stage, and region. The only key baseline characteristic that was not included was 'age'. Age was not included for three reasons: 1) age was reported as median and range in the RCTs, and therefore needs to be approximated as a normally distributed variable; however, age may not actually be normally distributed; 2) age was also reported as a binary variable but using different cut-offs across trials (65 years in KN671 and 75 years in AEGEAN); 3) age was very similar across trials (median age ranged from 63 to 66 years in AEGEAN, KN671, CM77T, and NADIM II) and was well-balanced across trial arms, thus leaving the variable unadjusted is considered reasonable.

Table 13 Comparison between base case and "all covariate" ML-NMR models: Hazard ratios for periNIVO+neoCT vs. periPEMBRO+neoCT

SA type	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months	60 months
EFS (4-knot M-spline proportional hazards)										
Base case covariates	[redacted]									
All covariates	[redacted]									
OS (1-knot M-spline proportional hazards)										
Base case covariates	[redacted]									
All covariates	[redacted]									

***Abbreviations**: EFS, event-free survival; ML-NMR, multilevel network meta-regression; OS, Overall survival*

Table 14 Comparison between base case and "all covariate" ML-NMR models: Hazard ratios for periNIVO+neoCT vs. periDURVA+neoCT

SA type	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months	60 months
EFS (4-knot M-spline proportional hazards)										
Base case covariates	[redacted]									
All covariates	[redacted]									
OS (1-knot M-spline proportional hazards)										
Base case covariates	[redacted]									
All covariates	[redacted]									

***Abbreviations**: EFS, event-free survival; ML-NMR, multilevel network meta-regression; OS, Overall survival*

Table 15 Comparison between base case and "all covariate" ML-NMR models: Hazard ratios for periNIVO+neoCT vs. neoCT

SA type	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months	60 months
EFS										
Base case covariates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All covariates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS										
Base case covariates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All covariates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: EFS, event-free survival; ML-NMR, multilevel network meta-regression; OS, Overall survival; PH, proportional hazards; SA, sensitivity analysis*

A5. Priority question. Please clarify if the ITCs reported in the company submission comprise only the three studies detailed in the submission or if a wider network of interventions and trials was used, with only the results for the nivolumab versus pembrolizumab presented in the company submission.

In the original submission, results were reported from three modelling approaches: a standard Bayesian NMA, a FP-NMA, and an ML-NMR. Due to time constraints, base case analyses under the three different approaches were conducted using the restricted subnetwork of trials described in the submission (CM77T, NADIM II, and KN671), while sensitivity and / or stratified analyses were based on the broader evidence base (the full network) as described in **Section 5.1**. **Table 16** provides a detailed breakdown of the networks used across all the models presented in the submission.

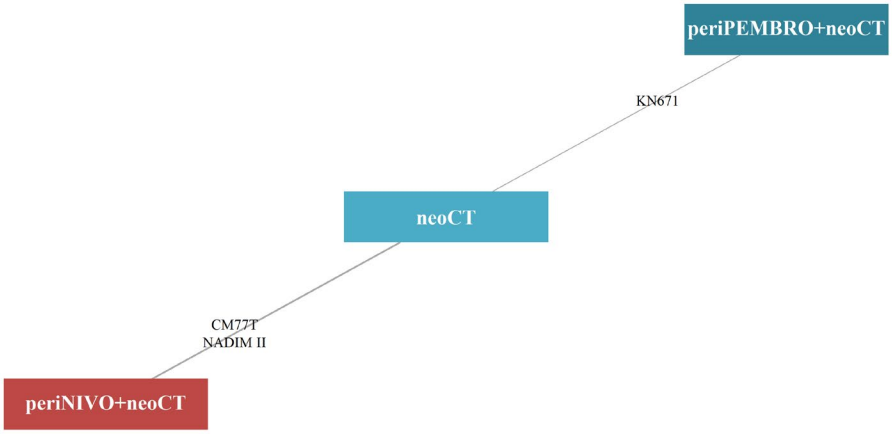
Due to the star-shaped network of evidence, the results from the subnetworks and the full network were largely consistent. This is because the key trial comparisons informing the estimates of interest (e.g., periPEMBRO+neoCT vs neoCT and periNIVO+neoCT vs neoCT) were the same in both the subnetwork (**Figure 39**) and the full network (**Figure 40**), and no intermediate evidence was present that could have influenced estimates for the comparisons of interest.

Table 16 Networks used across models presented in the original NICE submission report

Analytic framework	Outcome	Model type	Network	Section in submission
Standard Bayesian NMA	EFS	Base case	Subnetwork (**Figure 39**)	Section 5.2.1
		SA without NADIM II		Section 5.2.1.1
		Stratified by stage	Full network (**Figure 40**)	Section 5.2.1.1, Table 12
		SA with 2nd gen*		
		SA with resected**		
	OS	Base case	Subnetwork (**Figure 39**)	Section 5.2.2.1
		SA without NADIM II		Section 5.2.2.1.1
	pCR	Base case	Subnetwork (**Figure 39**)	Section 5.2.3
		SA without NADIM II		Section 5.2.3, Table 28
		Stratified by stage	Full network (**Figure 40**)	Section 5.2.3, Table 28
FP-NMA	EFS	Base case	Subnetwork (**Figure 39**)	Section 5.2.1.2
	OS	Base case		Section 5.2.2.2
ML-NMR	EFS	Base case	Subnetwork (**Figure 39**)†	Appendix 10.3.1.1
		Multiple SAs	Full network (**Figure 40**)	Appendix 10.4, Table 76
	OS	Base case	Subnetwork (**Figure 39**)†	Appendix 10.3.1.2

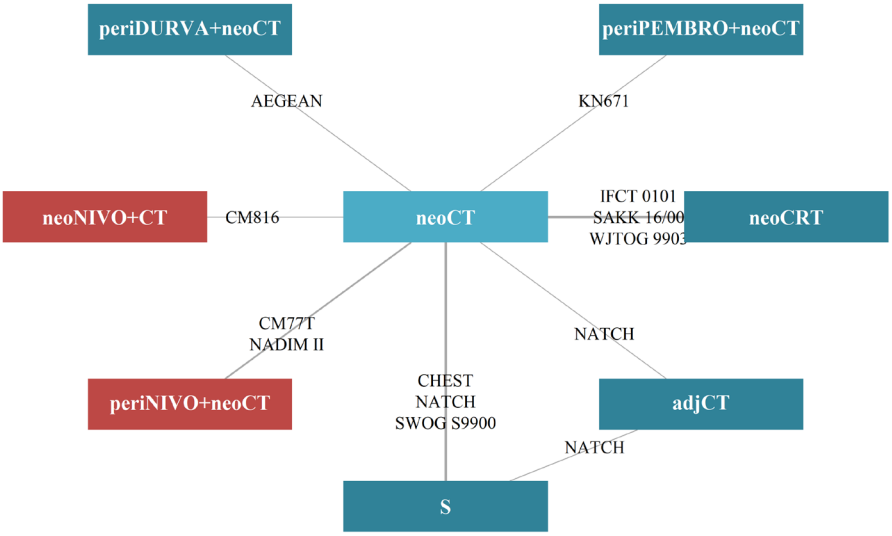
**Broadened eligibility from only third-generation platinum-based doublet chemotherapies in the base case to also include second-generation platinum-based regimens (see Section 4.1.4 of submission)*
***Broadened eligibility to include RCTs enrolling completely resected patients, as most adjCT trials were conducted in this population and restricting to resectable patients would have excluded nearly all relevant evidence for adjCT (see Section 4.1.4 of submission)*
†Model fit was assessed using the full network of evidence
***Note:** Green highlighting corresponds to models conducted on the full network*
***Abbreviations**: EFS, event-free survival; FP-NMA, fractional polynomial network meta-analysis; ML-NMR, multilevel network meta-regression; OS, overall survival; pCR, pathological complete response; SA, sensitivity analyses*

Figure 39 Subnetwork used in the original submission



Note: *The reference treatment is neoCT.*
Abbreviations*: neoCT, Neoadjuvant chemotherapy; neoNIVO+CT, Neoadjuvant nivolumab-chemotherapy; periNIVO+neoCT, perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, perioperative pembrolizumab-neoadjuvant chemotherapy.*

Figure 40 Full network used in the original submission



Note: *The reference treatment is neoCT.*
Abbreviations*: adjCT, Adjuvant chemotherapy; neoCRT, Neoadjuvant chemoradiotherapy; neoCT, Neoadjuvant chemotherapy; neoNIVO+CT, Neoadjuvant nivolumab-chemotherapy; periDURVA+neoCT, perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, perioperative pembrolizumab-neoadjuvant chemotherapy; S, Surgery.*

A6. Please conduct a fractional polynomial–NMA [FP-NMA] to compare nivolumab with pembrolizumab, and nivolumab with durvalumab using only data from CheckMate-77T (i.e., excluding the NADIM-II study), KEYNOTE-671 and the AEGEAN trial. If the company is unable to include the AEGEAN trial, then please conduct the requested

analyses including only CheckMate-77T and KEYNOTE-671, to enable a comparison of nivolumab versus pembrolizumab.

Please provide the results for fixed and random effects models for the following outcomes (including convergence plots and model fit statistics):

a) EFS using the most consistent outcome data from each trial. If sufficient data are available, please conduct separate analyses for:
   i) investigator-assessed EFS; and
   ii) BICR-assessed EFS.
b) Overall survival;
c) Time-to-treatment discontinuation.

Response of Question A6a) [EFS]

As described in the response to Question A3, while we acknowledge the EAG's concern regarding the mixing of BICR- and investigator-assessed outcomes, data limitations precluded the ability to conduct analyses using a uniform assessor.

An FP-NMA was conducted in the subnetwork of interest (**Figure 25**) using the data sources described in **Table 17**. Compared with the FP-NMA model presented in the original NICE submission report (**Section 5.2.1.2**), removal of NADIM II and inclusion of AEGEAN led to the selection of the following best-fitting NPH model (**Figure 41**), based on the pre-specified heuristic criteria (**Appendix Section 9.1**): a first-order Weibull-based fractional polynomial with powers [redacted], where treatment effects were applied to the first and third terms. The previously selected NPH model ([redacted]) remained a plausible alternative, with a DIC difference of [redacted] units. Results are therefore reported from the [redacted] model.

Table 17 Data sources informing the fractional polynomial network meta-analysis of EFS in the subnetwork of interest

Study	Stage*	Comparison	Kaplan-Meier curve data source
CM77T	II-IIIB (N2)	periNIVO+neoCT vs. neoCT	Data on file, DBL: Dec 16 2024
KN671**	II-IIIB (N2)	periPEMBRO+neoCT vs. neoCT	Majem ESMO IO 2024, DBL: Aug 19 2024
AEGEAN	II-IIIB (N2)	periDURVA+neoCT vs. neoCT	Heymach WCLC 2024, DBL: May 10 2024

** The brackets ("()") indicate a subset of the specified stage (e.g., Stage IIIB (N2)).*
***KEYNOTE 671 reported investigator assessed event-free survival, while CM77T and AEGEAN reported blinded independent central review.*
***Abbreviations**: CM77T, CM77T; DBL, database lock; IA, interim data; KN671, KEYNOTE-671; neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, perioperative pembrolizumab-neoadjuvant chemotherapy.*

Figure 41 Standardized DICs across evaluated models for EFS based on restricted network

1o PH model: *A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d0), but no shape parameters, resulting in a proportional hazards model;****1o NPH model:*** *A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d0), and the shape (i.e., time-related) parameter (d1); in this model, hazard ratios could vary over time;* ***2o PH model:*** *A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d0) but no shape parameters, resulting in a proportional hazards model;****2o NPH model:*** *A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d0) and one shape parameter (either d1 or d2); in this model, hazard ratios could vary over time;* ***2o NPH model (two shape)****: A second-order fractional polynomial in which treatment effects are placed on the scale parameter (d0) and both shape parameters, d1 and d2 (these are the highest complexity models that can be fit, and they tend to overfit the data, particularly on the tails of the survival curves, so these models were not considered suitable candidate models).*

Abbreviations: *DIC, deviance information criterion; EFS, event-free survival*

The HRs generated from the FP-NMA are plotted over time in **Figure 42**. HRs of periNIVO+neoCT relative to periPEMBRO+neoCT changed substantially [redacted], and subsequently stabilized, remaining constant over the remainder of the time period (up to [redacted] months). Whereas the comparison to periDURVA+neoCT is consistent over time.

Figure 42 Hazard ratios of periNIVO+neoCT vs comparators over time for EFS in the subnetwork of interest

Estimates obtained from the following model: P1=0 P2=-0.5; treatment effects on first (scale) and third (second shape) parameters. Dashed lines represent 95% credible intervals.
***Abbreviations**: neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, perioperative pembrolizumab-neoadjuvant chemotherapy*

Numerical HR estimates of periNIVO+neoCT vs comparators over 60 months are presented in **Table 18;** these were consistent with estimates generated by the standard Bayesian NMA. PeriNIVO+neoCT was associated with a statistically significantly lower risk of recurrence, progression or death relative to neoCT across all timepoints. With respect to the comparison between periNIVO+neoCT and periPEMBRO+neoCT, HRs trended away from the null but remained close to the null value of 1 over time, with CrIs becoming wider with increasing time.

Table 18 EFS hazard ratios of periNIVO+neoCT vs comparators over time in the subnetwork of interest

Time	EFS HR (95% CrI) for periNIVO+neoCT vs		
	periPEMBRO+neoCT	periDURVA+neoCT	neoCT
Fractional polynomial model			
3			
6			
12			
18			
24			
30			
36			
42			
48			
54			
60			

Time	EFS HR (95% CrI) for periNIVO+neoCT vs		
	periPEMBRO+neoCT	periDURVA+neoCT	neoCT
Constant HR model ***Fixed effect results from response to question A3***			
	[redacted]	[redacted]	[redacted]

***Notes**: HR < 1 favours periNIVO+neoCT; values in **bold** font are considered statistically significant (CrIs do not contain the null value). Estimates obtained from the following model: P1=0 P2=-0.5; treatment effects on first (scale) and third (second shape) parameters*
***Abbreviations**: CrI, credible interval; EFS, event-free survival; HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; periNIVO+neoCT, perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, perioperative pembrolizumab-neoadjuvant chemotherapy.*

The BGR and trace plots are presented in **Figure 47** and **Figure 48** respectively.

Figure 43 BGR diagnostic plots for EFS from the fractional polynomial NMA in the subnetwork of interest

[redacted]

***Note**: All plots show the shrink factor dropping quickly to ≈1.0 and staying flat indicating good convergence*

Figure 44 Trace plot of the parameter across the MCMC chains for EFS in the subnetwork of interest

***Note**: The overlapping, stable trajectories indicate good mixing and convergence to the target posterior distribution*

Response of Question A6b) [OS]

An FP-NMA was conducted in the subnetwork of interest (**Figure 25**) using the data sources described in **Table 17**. Compared with the FP-NMA model presented in the original NICE submission report (**Section 5.2.1.2**), removal of NADIM II and inclusion of AEGEAN led to the selection of the following best-fitting NPH model (**Figure 45)**, based on the prespecified heuristic criteria (**Appendix Section 9.1**): a first-order fractional polynomial with powers [redacted], where treatment effects were applied to the first and second terms. This model is consistent with the previously selected NPH model ([redacted], with treatment effects on the first and third terms) which remained a plausible alternative, with a DIC difference of [redacted] units.

The HRs generated from the FP-NMA are plotted over time in **Figure 46**. HRs of periNIVO+neoCT relative to periPEMBRO+neoCT changed substantially [redacted], and subsequently stabilized, remaining constant over the remainder of the time period (up to [redacted] months). Whereas the comparison to periDURVA+neoCT is consistent over time.

Figure 45 Standardized DICs across evaluated models for OS based on restricted network

1o PH model: *A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d0), but no shape parameters, resulting in a proportional hazards model;****1o NPH model:*** *A first-order fractional polynomial in which treatment effects were placed on the scale parameter (d0), and the shape (i.e., time-related) parameter (d1); in this model, hazard ratios could vary over time;* ***2o PH model:*** *A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d0) but no shape parameters, resulting in a proportional hazards model;****2o NPH model:*** *A second-order fractional polynomial in which treatment effects were placed on the scale parameter (d0) and one shape parameter (either d1 or d2); in this model, hazard ratios could vary over time;* ***2o NPH model (two shape)****: A second-order fractional polynomial in which treatment effects are placed on the scale parameter (d0) and both shape parameters, d1 and d2 (these are the highest complexity models that can be fit, and they tend to overfit the data, particularly on the tails of the survival curves, so these models were not considered suitable candidate models).*
Abbreviations: *DIC, deviance information criterion; OS, overall survival*

Figure 46 Hazard ratios of periNIVO+neoCT vs comparators over time for OS in the subnetwork of interest

Estimates obtained from the following model: P1=0 P2=-0.5; treatment effects on first (scale) and second (first shape) parameters. Dashed lines represent 95% credible intervals.
***Abbreviations**: neoCT, Neoadjuvant chemotherapy; periDURVA+neoCT, perioperative durvalumab-neoadjuvant chemotherapy; periNIVO+neoCT, perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, perioperative pembrolizumab-neoadjuvant chemotherapy*

Numerical HR estimates of periNIVO+neoCT vs comparators over 60 months are presented in **Table 18;** these were consistent with estimates generated by the standard Bayesian NMA. With respect to the comparison between periNIVO+neoCT and periPEMBRO+neoCT, HRs trended away from the null value of 1 over time, with CrIs becoming wider with increasing time. PeriNIVO+neoCT was associated with a lower risk of death relative to neoCT but with CrIs that crossed the null value across all timepoints.

Table 19 OS hazard ratios of periNIVO+neoCT vs comparators over time in the subnetwork of interest

Time	OS HR (95% CrI) for periNIVO+neoCT vs		
	periPEMBRO+neoCT	periDURVA+neoCT	neoCT
Fractional polynomial model			
3			
6			
12			
18			
24			
30			
36			
42			
48			
54			
60			
Constant HR model *Fixed effect results from response to question A3*			

Time	OS HR (95% CrI) for periNIVO+neoCT vs		
	periPEMBRO+neoCT	periDURVA+neoCT	neoCT
	[redacted]	[redacted]	[redacted]

Notes: *HR < 1 favours periNIVO+neoCT; values in **bold** font are considered statistically significant (CrIs do not contain the null value). Estimates obtained from the following model: P1=0 P2=-0.5; treatment effects on first (scale) and second (first shape) parameters*
Abbreviations: *CrI, credible interval; HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; OS,overall survival; periNIVO+neoCT, perioperative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, perioperative pembrolizumab-neoadjuvant chemotherapy.*

The BGR and trace plots are presented in **Figure 47** and **Figure 48** respectively.

Figure 47 BGR diagnostic plots for overall survival from the fractional polynomial NMA in the subnetwork of interest

[redacted]

Note: *All plots show the shrink factor dropping quickly to ≈1.0 and staying flat indicating good convergence*

Figure 48 Trace plot of the parameter across the MCMC chains for OS in the subnetwork of interest

***Note**: The overlapping, stable trajectories indicate good mixing and convergence to the target posterior distribution*

Response of Question A6c) [Time-to-treatment discontinuation]

No analysis could be conducted including KN671 or AEGEAN, as this outcome was not reported in either study.

A7. Please clarify if the full intention-to-treat (ITT) population from KEYNOTE-671, including patients with ALK rearrangements and EGFR mutations, was used for the ITCs presented in the company submission, and if so, please clarify what impact this is likely to have on the results of the ITCs.

The majority of the ITCs presented in the submission were based on the subnetwork of CM77T, NADIM II, and KN671 (**Figure 39**). Patients with EGFR+ or ALK+ tumours were excluded from CM77T and NADIM II; however, in CM77T, testing was only mandatory for patients with non-squamous histology in Asian regions, and thus some patients with these mutations may have been enrolled. In KN671, EGFR and ALK testing was left to investigator discretion, and mutation status was unreported for the majority of patients. Approximately 4% of patients had EGFR+ tumours and 3% had ALK+ tumours. Because the primary efficacy analyses in KN671 were conducted in the ITT population, and only a very small number of patients had EGFR mutations or ALK translocations, the ITCs presented in the submission were also based on the ITT population.

For EGFR mutations, subgroup analyses from KN671 (**Table 20**) show that although point estimates for EFS and OS are further from the null in patients with EGFR+ mutations, the confidence intervals overlap with those of the ITT population. Given the small sample size (4% of the KN671 population) and wide confidence intervals, excluding EGFR+ patients would be unlikely to have materially affected the ITC findings.

For ALK translocations, subgroup analyses from KN671 (**Table 20**) indicate that EFS and OS outcomes in patients without ALK translocations were comparable to those in the ITT population. As patients with ALK translocations represented only 3% of the KN671 population and had similar point estimates, their exclusion would likewise be unlikely to have materially affected the ITC findings.

Table 20 EFS and OS survival from KN671 in the ITT and EGFR/ALK subgroups

Outcome	Subgroups	Events/Patients		PeriPEMBRO+neoCT vs neoCT Hazard ratio (95% CI)
		Pembro	Placebo	
EFS	Overall (ITT)	[redacted]	[redacted]	[redacted]
	EGFR mutation status: Yes	[redacted]	[redacted]	[redacted]
	EGFR mutation status: No	[redacted]	[redacted]	[redacted]
	EGFR mutation status: Unknown	[redacted]	[redacted]	[redacted]
	ALK translocation: No	[redacted]	[redacted]	[redacted]
	ALK translocation: Unknown	[redacted]	[redacted]	[redacted]
OS	Overall (ITT)	[redacted]	[redacted]	[redacted]

Outcome	Subgroups	Events/Patients		PeriPEMBRO+neoCT vs neoCT Hazard ratio (95% CI)
		Pembro	Placebo	
	EGFR mutation status: Yes	[redacted]	[redacted]	[redacted]
	EGFR mutation status: No	[redacted]	[redacted]	[redacted]
	EGFR mutation status: Unknown	[redacted]	[redacted]	[redacted]
	ALK translocation: No	[redacted]	[redacted]	[redacted]
	ALK translocation: Unknown	[redacted]	[redacted]	[redacted]

***Abbreviations**: ALK, anaplastic lymphoma kinase; CI, confidence interval; EFS, event-free survival; EGFR, epidermal growth factor receptor; ITT, intention-to-treat; OS, overall survival.*

In AEGEAN, a protocol amendment led to the exclusion of patients with EGFR+ or ALK+ tumours from the modified ITT population, although those enrolled prior to the amendment remained included. As with KN671, the inclusion of patients with ALK translocations/EGFR mutations in AEGEAN would have unlikely impacted the ITC results.

CheckMate-77T

A8. Priority question. With regards to diagnosing ALK rearrangements and EGFR mutations in CheckMate-77T, please:

a) **clarify whether all patients were required to be tested for ALK rearrangements and EGFR mutation status at baseline/prior to enrolment in CheckMate-77T and prior to commencement of neoadjuvant treatment.**
b) **provide details of the tests used to diagnose ALK rearrangements and EGFR mutations in CheckMate-77T.**
c) **clarify if the testing and timing of tests to diagnose ALK rearrangements and EGFR mutations in CheckMate-77T are consistent with that currently done in clinical practice in England.**

a) Per study protocol CheckMate-77T exclusion criteria the below patients were excluded from the study:
- participants with EGFR mutation regardless of mutation type. *EGFR* testing was mandatory in all patients with NSQ histology.
- Participants with known ALK mutations. *ALK* testing was done in patients with history of *ALK* alterations

b) Participants must have the above mutation tests performed at the screening phase of the study. Historical results obtained as standard of care prior to screening period were deemed acceptable. If a patient were found to have one or more EGFR or ALK mutations, they were excluded from the study.

c) We will follow-up with a response to this question on 10th September as agreed in the clarification meeting.

A9. Priority question. Please provide a table with the serious adverse events experienced by each treatment arm in CheckMate-77T.

A table of serious adverse events by each treatment arm, per the latest DBL (Dec 24), is appended to this response document ('appendix 1').

A10. Priority question. Please provide the results for investigator-assessed EFS and progression-free survival from CheckMate-77T including median values (with accompanying 95% confidence interval [95% CI]) for each trial arm and the resulting hazard ratio with 95% CI for the comparison of nivolumab versus chemotherapy.

PFS is not a relevant/captured outcome for the CheckMate-77T trial. Investigator-assessed EFS is provided below. Note that median EFS was not reached in the nivolumab + chemotherapy arm.

[redacted]

A concordance analysis of EFS-BICR vs EFS-INV was conducted based on the primary analysis, with [redacted] concordance between BICR and INV for events and censoring. More events were identified in BICR (event BICR/INV = [redacted]

A11. Priority question. Please provide:

a) **a table with a breakdown of all subsequent treatments received by patients in CheckMate-77T, including details of chemotherapy regimens and any combination therapies.**
b) **a table detailing the first subsequent treatments received by patients in CheckMate-77T, including combination therapies.**
c) **a table detailing the second subsequent treatments received by patients in CheckMate-77T, including combination therapies.**

The CheckMate-77T electronic Case Report Form (eCRF) collected subsequent treatments only at the agent level. Deriving a combination at the regimen level will require the development of a rule-based algorithm, which may not be accurate. Subsequent treatments were not measured at the granularity of second subsequent treatments. We have provided a table with a breakdown of a) all subsequent treatments ('appendix 2'), and b) first subsequent treatments ('appendix 3'), received by patients CheckMate-77T at the agent level.

A12. Please provide subgroup results for overall survival by subsequent treatments received by patients in CheckMate-77T.

It is not feasible to provide overall survival results by subsequent treatments at the regimen level received by patients in CheckMate-77T.

A13. Please clarify when the results of the next analysis of OS from CheckMate-77T is expected.

The database lock for the final OS analysis is anticipated in Q1 2026. Note that the database lock is event-driven and the database will be locked when 174 deaths have occurred.

Clinical study reports

A14. Please provide:

a) the full clinical study report (CSR) for CheckMate-77T, [redacted]

b) [redacted]

The CSR and associated appendices have been provided as an appendix to this response document.

A15. Please provide the CSR including the results for the interim analysis of overall survival from CheckMate-77T.

The interim analysis of overall survival was not a pre-planned database analysis, therefore the CSR, dated 10th November 2023, has not been updated with the interim analysis of overall survival from CheckMate-77T.

Subgroups

A16. Priority question. Please provide a forest plot with accompanying hazard ratios and 95% confidence intervals in all subgroups in CheckMate-77T [redacted] for the following outcomes:

a) **EFS per investigator assessed; and**
b) **Overall survival.**

A forest plot with accompanying hazard ratios and 95% confidence intervals in all subgroups in CheckMate-77T for EFS-INV has been appended ('[redacted]') to this response document.

OS results continue to mature and have not been provided for all subgroups accordingly. OS by trial stratification factor subgroups has been provided below. Note that the OS information fraction remains very low at the time of the interim OS analysis and therefore results should be interpreted with caution.

[redacted]

A17. Priority question. Please provide the results for the Europe subgroup in CheckMate-77T for all outcomes.

Outcomes have been provided for EFS and OS.

EFS:

- per investigator: provided in response to A16A (‘appendix 4’).
- Per BICR:

[redacted]

OS:

Results should be interpreted with caution. The OS information fraction is small as results continue to mature, and 'region' is not a trial stratification factor.

[redacted]

NADIM-II

A18. Please explain the clinical rationale for why [redacted]

Cross-trial comparisons should be made with caution due to differences in study design, patient population, event rates, and statistical power.

Patient population: NADIM II exclusively enrolled patients with stage IIIA NSCLC, a group with a high risk of recurrence and death, where the impact of effective therapy may be more pronounced. CheckMate 77T included a broader population (stage II–IIIB) of resectable NSCLC. In addition, in NADIM II, patients in the experimental group included those who had R0 resection and then received 6 months of adjuvant nivolumab vs the control group where patients received chemotherapy alone followed by surgery. In CheckMate 77T, per protocol, patients in the experimental arm received adjuvant nivolumab after surgery and neoadjuvant nivolumab plus chemotherapy regardless of completeness of resection. Additionally, R0 resection status was not a stratification factor in CheckMate 77T.

Study design and sample size: NADIM II was a Spain-only smaller study and it is known that small studies can sometimes lead to larger observed effect sizes and statistical significance, especially if the population is more homogeneous. On the other hand, CheckMate 77T was a global study with diverse patient population that can potentially result in variability in patient outcomes.

Statistical Power and Endpoints: The primary endpoint in NADIM II was pCR and the secondary endpoints were PFS and OS at 24-months. In CheckMate 77T, EFS was primary endpoint and pCR, MPR, and OS were key secondary endpoints. Consequently, the studies are powered differently and the threshold for detecting statistical significance and the number of events required to reach it varies between the studies.

Hence, [redacted]

Section B: Clarification on cost-effectiveness data

B1. Priority question. Please provide a scenario comparing the cost of nivolumab to durvalumab. Please use the AEGEAN study to inform the durvalumab dosing regime.

As outlined in the company submission, BMS consider perioperative pembrolizumab to be the standard of care treatment for patients with resectable NSCLC in England, and thus believe that the most relevant comparator for cost comparison decision-making is perioperative pembrolizumab. Further to confirmation from NICE during the clarification meeting that an approach of comparing nivolumab to the single comparator of perioperative pembrolizumab is appropriate, a comparison with durvalumab has not been included.

B2. Priority question. If the ITC requested in clarification question A3 identifies a significant difference in treatment discontinuation, please conduct a scenario in which the number of treatment cycles reflect the difference in TTD.

If TTD data is not available, please provide any available data to justify the assumption of no difference in TTD between treatments.

BMS have been unable to locate any TTD data for KEYNOTE-671; therefore, we are not able to conduct the requested scenario analysis.

In support of the assumption that there is no difference in TTD between treatments, we would highlight the similar treatment effects underlying this cost minimisation analysis. If there had been a substantial difference in TTD, it is likely that this would also be reflected in a significant variation in treatment effect. As previously mentioned, we have found no TTD data for KEYNOTE-671. However, in the KEYNOTE-671 trial, treatment-related adverse events leading to discontinuation of all trial treatments occurred in 12.6% of participants in the pembrolizumab arm, compared with 19.3% of patients treated with nivolumab in the CheckMate-77T study experiencing adverse events leading to treatment discontinuation. While these figures may not directly represent TTD due to the potential influence of event timing, they do suggest that discontinuation rates could be expected to be relatively similar, or perhaps slightly higher, for nivolumab. Therefore, the current assumption of equivalent TTD may be considered conservative.

B3. Priority question. While the EAG appreciates that the company is committed to providing nivolumab at a similar cost to pembrolizumab with a PAS applied; Please provide a company scenario which includes the PAS for nivolumab approved for TA876. If the company considers that the PAS for nivolumab in this indication would be different to TA876, please use the more appropriate PAS.

Scenario results using the current nivolumab PAS of [redacted] are presented in the table below.

Table 1. Base-case results with nivolumab PAS

	Acquisition costs	Administration costs	TOTAL COSTS	Difference
Perioperative nivolumab	[redacted]	£3,726.47	[redacted]	
Perioperative pembrolizumab	£89,420.00	£2,480.93	£91,900.93	[redacted]

B4. Priority question. According to the EAG's clinical experts, the administration of pembrolizumab in an adjuvant setting may be quite varied, with some patients being treated with eight cycles of 400mg Q6W, and others receiving three cycles of 200mg Q3W and then six cycles of 400mg Q6W. Please provide a scenario analysis exploring these alternative dosing and administration frequency assumptions.

Scenario results reflecting these alternative dosing schedule for pembrolizumab has been provided below as requested.

Table 1. Adjuvant administration of pembrolizumab eight cycles of 400mg Q6W

	Acquisition costs	Administration costs	TOTAL COSTS	Difference
Perioperative nivolumab	£84,288.00	£3,726.47	£88,014.47	
Perioperative pembrolizumab	£105,200.00	£2,688.52	£107,888.52	-£19,874.05

Table 2. Adjuvant administration of pembrolizumab three cycles of 200mg Q3W and then six cycles of 400mg Q6W

	Acquisition costs	Administration costs	TOTAL COSTS	Difference
Perioperative nivolumab	£84,288.00	£3,726.47	£88,014.47	
Perioperative pembrolizumab	£99,940.00	£2,896.11	£102,836.11	-£14,821.64

B5. Priority question. The EAG notes that in TA1017, the administration costs were informed using NHS reference codes SB12Z and SB13Z from the Healthcare Resource Group (HRG) sheet, while it appears the same cost codes from the Outpatient Procedure (OPROC) sheet have been used to inform the company base case administration costs. Please can the company confirm that the OPROC costs have been used, and if so, justify their use given the greater activity logged using these cost codes from the Admitted Patient Care (APC) sheet. The EAG notes that the HRG sheet collates activities across all cost sheets, including OPROC and APC. Additionally, please conduct a scenario using the HRG costs.

Scenario results reflecting HRG administration costs has been provided below as requested.

Table 1. Adjuvant administration of pembrolizumab with HRG Administration costs

	Acquisition costs	Administration costs	TOTAL COSTS	Difference
Perioperative nivolumab	£84,288.00	£7,160.01	£91,448.01	
Perioperative pembrolizumab	£89,420.00	£4,795.02	£94,215.02	-£2,767.01

B6. Priority question. Noting that cost codes SB12Z and SB13Z relate to the administration of simple and complex chemotherapies at first attendance, please conduct a scenario in which SB12Z and SB13Z are used to cost initial administrations of treatments and then SB15Z (Deliver Subsequent Elements of a Chemotherapy Cycle) is used to cost subsequent administrations. Please conduct the scenarios using the HRG and OPROC costs outlined in clarification question B3.

Scenario results reflecting HRG and OPROC administration costs with SB15z

Table 1. Adjuvant administration of pembrolizumab with HRG Administration costs, Subsequent Elements of a Chemotherapy Cycle SB15Z

	Acquisition costs	Administration costs	TOTAL COSTS	Difference
Perioperative nivolumab	£84,288.00	£7,356.75	£91,644.75	
Perioperative pembrolizumab	£89,420.00	£4,775.30	£94,195.30	-£2,550.55

Table 2. Adjuvant administration of pembrolizumab with OPROC Administration costs Subsequent Elements of a Chemotherapy Cycle SB15Z

	Acquisition costs	Administration costs	TOTAL COSTS	Difference
Perioperative nivolumab	£84,288.00	£3,676.90	£87,964.90	
Perioperative pembrolizumab	£89,420.00	£2,337.66	£91,757.66	-£3,792.76

B7. Priority question. In Table 26 of the company submission, the pembrolizumab administration costs over the full time horizon has been calculated at £1,245.54. Given an individual administration cost of £256.95, the EAG notes that the full time horizon cost reflects six administrations, opposed

to the seven administrations outlined in the submission (one 200mg administration and six 400mg administrations). Can the company confirm that seven administrations should have been costed for and provide an updated base case as necessary.

Seven administrations should have been included. The results in the submission has been updated to reflect this and amended versions of Document A and Document B have been appended to this response document.

B8. Priority question. Please inflate costs derived from the National Cost Collection for the NHS from 2024 to the current year.

Given that the inflation index for 2025 isn't yet available we aren't able to provide this update.

B9. In Section B.4.6 of the company's submission, it's stated that "the list price comparison of perioperative nivolumab + neoadjuvant chemotherapy against perioperative pembrolizumab + neoadjuvant chemotherapy yielded incremental cost-saving of £2,846.78". Please can the company share how this cost-saving was calculated.

The MS Excel cost calculator used for estimating the costs in this cost comparison have been shared as an appendix to this response document.

1) The log cumulative hazard plots and Schoenfeld residuals used to assess proportional hazards in CheckMate-77T and KEYNOTE-671 for EFS as detailed in Section 4.4.2 of the NMA report.

For EFS, the log cumulative hazard plots and Schoenfeld residuals for CheckMate-77T (CM77T) and KEYNOTE-671 (KN671) can be found in **Figure 1** and **Figure 2** respectively.

Figure.7.Log.cumulative.hazard.plots.and.Schoenfeld.residuals.for.CM❸❸T.for.event_free.survival

A¡ Log.cumulative.hazard.plot B¡ Schoenfeld.residuals…

Data.cut.off¿DEC7❷8680.(Source¿Data.on.file)
Abbreviations¿neoCT?Neoadjuvant.chemotherapy·.periNIVO>neoCT?perioperative.nivolumab_neoadjuvant.chemotherapy

Figure.8.Log.cumulative.hazard.plots.and.Schoenfeld.residuals.for.KN2☒7.for.event_free.survival

A¡ Log.cumulative.hazard.plot B¡ Schoenfeld.residuals...

Data.cut.off¿AUG7☒8680.(Source¿Majem.IO.ESMO.8680)

Abbreviations¿neoCT?Neoadjuvant.chemotherapy·.periPEMBRO>neoCT?perioperative.pembrolizumab_neoadjuvant.chemotherapy

2) The Kaplan-Meier (KM) data, log cumulative hazard plots, Schoenfeld residuals, and Grambsch-Therneau tests used to assess proportional hazards in CheckMate-77T and KEYNOTE-671 for the analysis of OS (Section 4.4.2 of the NMA report).

For OS, the KM data can be for CM77T and KN671 can be found in **Figure 3** and **Figure 4** respectively.

Figure.9.Kaplan_Meier.curves.of.overall.survival.for.CM77T.

Data.cut.off¿DEC7 8680.(Source¿Data.on.file)
Abbreviations¿OS?overall.survival·.neoCT?Neoadjuvant.chemotherapy·.periNIVO>neoCT?perioperative.nivolumab_neoadjuvant.chemotherapy¡

Figure.0.Kaplan_Meier.curves.of.overall.survival.for.KN237.

Data.cut.off¿AUG76,8680.(Source¿Majem.IO.ESMO.8680)
Abbreviations¿OS?overall.survival·.neoCT?Neoadjuvant.chemotherapy·.periPEMBRO>neoCT?perioperative.pembrolizumab_
neoadjuvant.chemotherapy¡

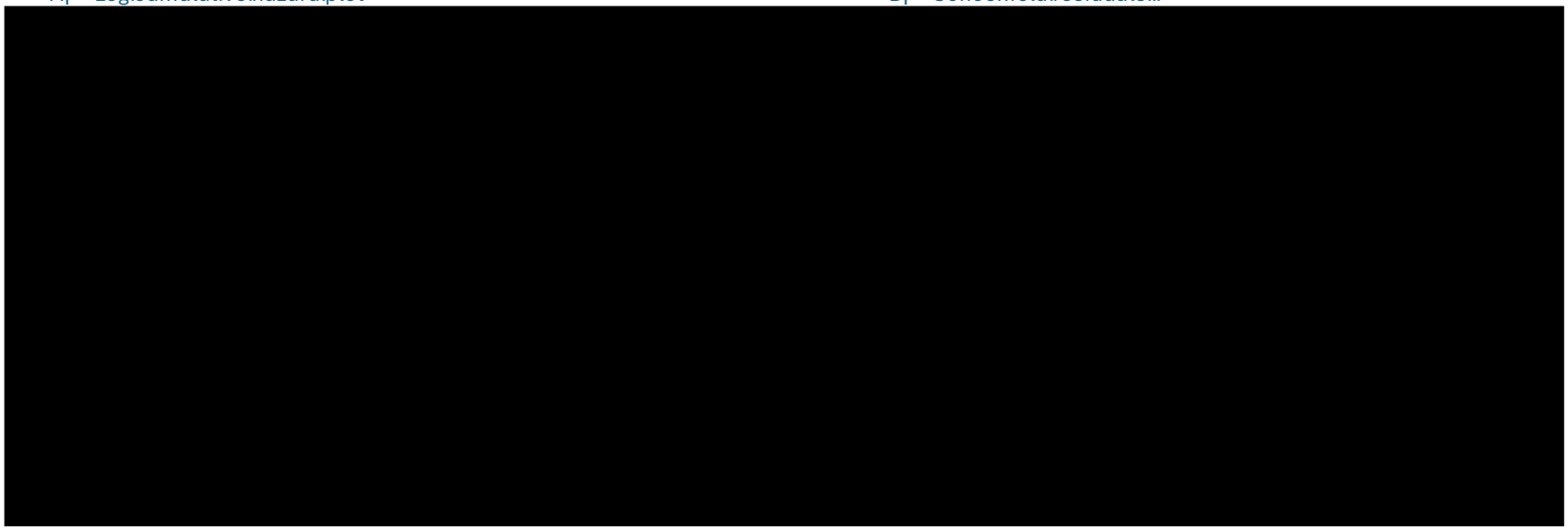
For overall survival, the log cumulative hazard plots and Schoenfeld residuals for CheckMate-77T (CM77T) and KEYNOTE-671 (KN671) can be found in **Figure 4** and **Figure 5** respectively.

Figure.❶.Log.cumulative.hazard.plots.and.Schoenfeld.residuals.for.CM❼❼T.for.overall.survival
A¡ Log.cumulative.hazard.plot B¡ Schoenfeld.residuals…

Data.cut.off¿DEC7❷8680.(Source¿Data.on.file)
Abbreviations¿neoCT?Neoadjuvant.chemotherapy·.periNIVO>neoCT?perioperative.nivolumab_neoadjuvant.chemotherapy¡

Figure.2.Log.cumulative.hazard.plots.and.Schoenfeld.residuals.for.KN-937.for.overall.survival

A¡ Log.cumulative.hazard.plot B¡ Schoenfeld.residuals...



Data.cut.off¿AUG.2023.(Source¿Majem.IO.ESMO.2023)

Abbreviations¿neoCT?Neoadjuvant.chemotherapy·.periPEMBRO>neoCT?perioperative.pembrolizumab_neoadjuvant.chemotherapy

3) For the indirect treatment comparisons reported in the company's response to clarification questions, please provide KM data, log cumulative hazard plots, Schoenfeld residuals, and Grambsch-Therneau tests to assess proportional hazards in:
    a. CheckMate-77T for EFS per investigator assessment (EFS-inv);

For EFS as assessed by the investigator, the KM data for CM77T can be found in **Figure 7**.

Figure.❸Kaplan_Meier.curves.of.event_free.survival.(as.assessed.by.the.investigator).for.CM❸❸T.

Data.cut.off¿DEC7❷8680.(Source¿Data.on.file)
Abbreviations¿EFS?event_free.survival·.neoCT?Neoadjuvant.chemotherapy·.periNIVO>neoCT?perioperative.nivolumab_neoadjuvant.chemotherapy¡

For EFS as assessed by the investigator, the log cumulative hazard plots and Schoenfeld residuals for CM77T can be found in **Figure 8**.

Figure.❹Log.cumulative.hazard.plots.and.Schoenfeld.residuals.for.CM❸❸T.for.event_free.survival.(as.assessed.by.the.investigator)
A¡ Log.cumulative.hazard.plot B¡ Schoenfeld.residuals...

Data.cut.off¿DEC7❷8680.(Source¿Data.on.file)
Abbreviations¿neoCT?Neoadjuvant.chemotherapy·.periNIVO>neoCT?perioperative.nivolumab_neoadjuvant.chemotherapy¡

b. KEYNOTE-671 for EFS per blinded independent central review (EFS-BICR);

For EFS as assessed by BICR, the KM data for KN671 can be found in **Figure 9**.

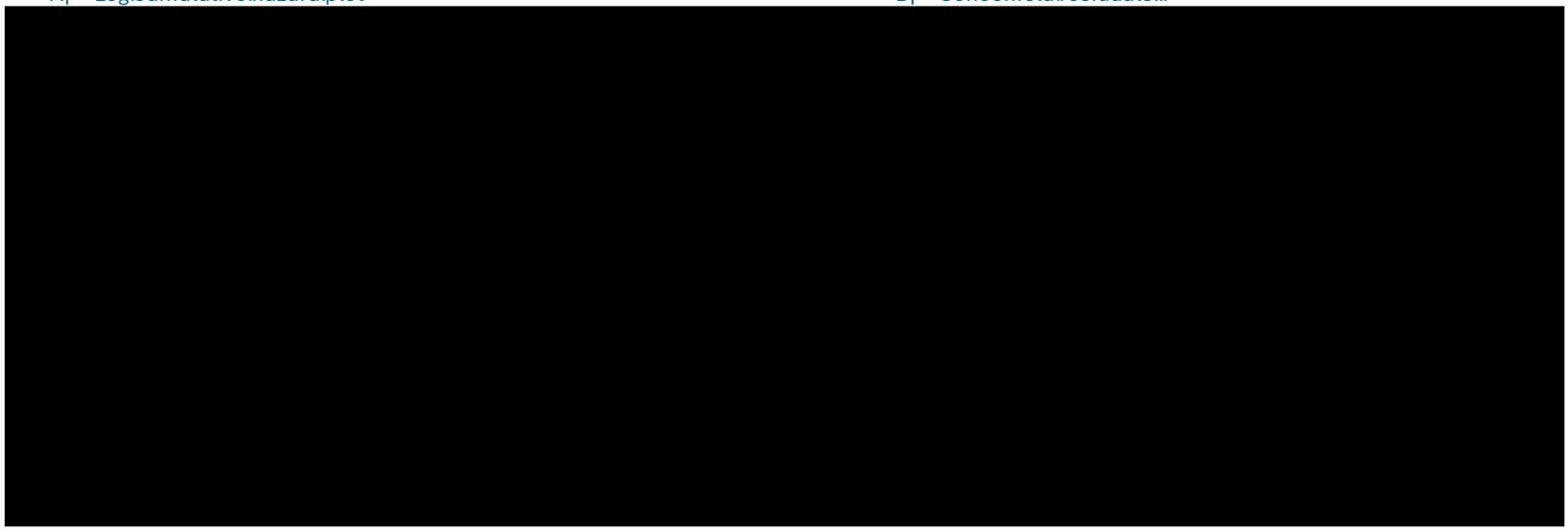
Figure.9.Kaplan_Meier.curves.of.event_free.survival.(as.assessed.by.blinded.independent.central.review).for.KN671.

Data.cut.off¿8.JUL8688.(Source¿Keytruda.EPAR·.88.February.8680?.Figure.76)
Abbreviations¿EFS?event_free.survival·.neoCT?Neoadjuvant.chemotherapy·.periPEMBRO>neoCT?perioperative.pembrolizumab_neoadjuvant.chemotherapy¡

For EFS per BICR, the log cumulative hazard plots and Schoenfeld residuals for KN671can be found in **Figure 10**.

Figure.76.Log.cumulative.hazard.plots.and.Schoenfeld.residuals.for.KN6☒7.for.event_free.survival.(as.assessed.by.blinded.independent.central.review)

A¡ Log.cumulative.hazard.plot B¡ Schoenfeld.residuals…



Data.cut.off¿8☒UL8688.(Source¿Keytruda.EPAR·.88.February.8680?.Figure.76)

Abbreviations¿neoCT?Neoadjuvant.chemotherapy·.periPEMBRO>neoCT?perioperative.pembrolizumab._neoadjuvant.chemotherapy¡

c. AEGEAN for the analyses of EFS-inv, EFS-BICR and OS.

Very limited data are available with respect to EFS per investigator from AEGEAN. The only relevant evidence identified came from the EPAR, where only the HR was reported (based on the database lock of 27 February 2022), but the corresponding KM data was not presented. As a result, the KM plots and PH assessment figures could not be generated.

For EFS by BICR, the KM data for AEGEAN can be found in **Figure 11**.

Figure.77.Kaplan_Meier.curves.of.event_free.survival.(as.assessed.by.blinded.independent.central.review).for.AEGEAN.

Data.cut.off¿MAY768680.(Source¿Heymach.WCLC.8680)
Abbreviations¿EFS?event_free.survival·.neoCT?Neoadjuvant.chemotherapy·.periDURVA>neoCT?perioperative.durvalumab_neoadjuvant.chemotherapy¡

For EFS per BICR, the log cumulative hazard plots and Schoenfeld residuals for AEGEAN can be found in **Figure 12**.

Figure.78.Log.cumulative.hazard.plots.and.Schoenfeld.residuals.for.AEGEAN.for.event_free.survival.(as.assessed.by.blinded.independent.central.review)
A¡ Log.cumulative.hazard.plot B¡ Schoenfeld.residuals…

Data.cut.off¿MAY768680.(Source¿Heymach.WCLC.8680)
Abbreviations¿neoCT?Neoadjuvant.chemotherapy·.periDURVA>neoCT?perioperative.durvalumab_neoadjuvant.chemotherapy¡

For OS, the KM data for AEGEAN can be found in **Figure 13**.

Figure.79.Kaplan_Meier.curves.of.overall.survival.for.AEGEAN.

Data.cut.off¿MAY768680.(Source¿Heymach.WCLC.8680)
Abbreviations¿OS?overall.survival·.neoCT?Neoadjuvant.chemotherapy·.periDURVA>neoCT?perioperative.durvalumab_neoadjuvant.chemotherapy¡

For OS, the log cumulative hazard plots and Schoenfeld residuals for AEGEAN can be found in **Figure 14.**

Figure.70.Log.cumulative.hazard.plots.and.Schoenfeld.residuals.for.AEGEAN.for.overall.survival)
A¡ Log.cumulative.hazard.plot B¡ Schoenfeld.residuals…

Data.cut.off¿MAY768680
Abbreviations¿neoCT?Neoadjuvant.chemotherapy·.periDURVA>neoCT?perioperative.durvalumab␣neoadjuvant.chemotherapy¡

4) When running the NMA R code we get the following error message: "cannot open compressed file 'Model data/EFS, periPEMBRO only/data.rda', probable reason 'No such file or directory'". Of the files provided by the company, there is no folder titled "EFS, periPEMBRO". Accordingly it is not clear to the EAG whether all required data (e.g., data.rda files) have been provided. Please provide fully working NMA R code with the appropriate data files to enable the EAG to validate the company's analyses.

The NMA R code has been updated to resolve this error. Please refer to the updated folder titled “NMA.code.files” in the zipped folder.

5) For the FP-NMAs, the code provided by the company comprises some txt files that the EAG believes comprise WinBUGS code. The EAG anticipates that these files are called by an R script, but the company has not provided any R code for the FP-NMAs. As such, please clarify the statistical package used to run the FP-NMAs and provide working code and data for the FP-NMAs.

We have now shared the additional R files. They are embedded within the folder entitled “FP.code.files” in the zipped folder.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6310]

Clarification questions

August 2025

File name	Version	Contains confidential information	Date
ID6310 nivolumab CC clarification questions response A8_C	1.0	no	14/09/2025

CheckMate-77T

A8. Priority question. With regards to diagnosing ALK rearrangements and EGFR mutations in CheckMate-77T, please:

a) clarify whether all patients were required to be tested for ALK rearrangements and EGFR mutation status at baseline/prior to enrolment in CheckMate-77T and prior to commencement of neoadjuvant treatment.
b) provide details of the tests used to diagnose ALK rearrangements and EGFR mutations in CheckMate-77T.
c) clarify if the testing and timing of tests to diagnose ALK rearrangements and EGFR mutations in CheckMate-77T are consistent with that currently done in clinical practice in England.

C. As agreed in the clarification meeting the response to this question was extended to 10th September. Use of an FDA approved, or local Health Authority-approved test (tissue or blood) was used for ALK and EGFR mutation testing in CM77T. This would be consistent with mutation testing in the England in which ALK rearrangements are identified using IHC and EGFR by NGS or single gene PCR testing. As discussed with a clinical expert (St Barts Hospital, London), the timing and tests used in CM77T, align with routine clinical practice within England

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6310]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK. The charity is funded by registration fees and sponsorship
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	BTOG 2024- April Platinum Sponsorship £30,000 + VAT BTOG 2025- March Platinum Sponsorship £30,000 + VAT
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To increase the chance of cure
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The measure here would be an improvement in EFS (hazard ratio of 0.7 or better)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes there is a significant unmet need to improve cure rates for resected NSCLC

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Either surgery alone Neoadjuvant treatment and surgery Surgery and adjuvant treatment Surgery and peri-operative treatment

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Treatment is guided by reimbursement
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is a lot of variability in treatment for early stage / resectable NSCLC
9c. What impact would the technology have on the current pathway of care?	It would provide another treatment option
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	n/a
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Centres where SACT is delivered
10c. What investment is needed to introduce the technology? (For example,	n/a

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	N/a

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	N/a

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Disease recurrence or toxicities could lead to discontinaution
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	n/a
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – more patients will be cured
16a. Is the technology a 'step-change' in the	Yes

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – although there are other technologies in this space now
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are effective algorithms for managing toxicities in place

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	EFS pCR OS
18c. If surrogate outcome measures were used, do they adequately predict	Yes

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	n/a
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	n/a
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	n/a
21. How do data on real-world experience compare with the trial data?	n/a

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	n/a

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Unmet need to improve cure for resected / early stage NSCLC • Peri-operative strategies are game changing for improving outcomes for this population • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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BMJ TAG

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6310]

Cost-comparison Technology Appraisal

Source of funding
This report was commissioned by the NIHR Evidence Synthesis Programme as project number 175635.

Title:	Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer
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Date completed:	26/09/2025
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 175635.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Nadia Yosaf (Consultant Thoracic Medical Oncologist, The Royal Marsden Hospital), Dr Pooja Bhatnagar (Consultant Clinical Oncologist, Leeds Teaching Hospitals Trust) and Dr Zacharias Tasigiannopoulos (Consultant Clinical Oncologist, Norfolk and Norwich University Hospitals) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Bacelar M, Wakefield V, Walters A, Dadswell C, Edwards SJ, Burgess B. Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer: A Cost-comparison Technology Appraisal. BMJ Technology Assessment Group, 2025.

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Mariana Bacelar	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report.
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Clare Dadswell	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Ben Burgess	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

Table of Contents 4

List of Tables 7

List of Figures 10

List of Abbreviations 11

1 Executive summary 13

2 Background 16

3 Critique of the decision problem in the company's submission 19

3.1 Population 26

3.2 Intervention 28

3.3 Comparators 29

3.4 Outcomes 31

4 Summary of the EAG's critique of clinical effectiveness evidence submitted 34

4.1 Critique of the methods review 34

4.2 Critique of trials of the technology of interest 36

4.3 Clinical effectiveness results 40

4.3.1 CheckMate-77T 40

4.3.2 NADIM-II 46

4.3.3 Subgroup analyses 46

4.4 Critique of the indirect treatment comparison 48

4.4.1 Critique of trials identified and included in the indirect treatment comparison 48

4.4.2 Critique of the methods used for the indirect treatment comparison 52

4.4.3 Traditional Bayesian network meta-analysis 54
4.4.4 Fractional polynomial network meta-analysis 55
4.4.1 Multilevel network meta-regression 58
4.5 Additional work on clinical effectiveness undertaken by the EAG 62
4.5.1 EAGs Bucher ITCs 62
4.5.2 EAGs point-and-density plots 63
4.6 Adverse effects 68
4.7 Conclusions of the clinical effectiveness section 70
5 Summary of the EAG's critique of cost comparison evidence submitted 75
5.1 Cost assumptions 75
5.1.1 EAG critique 75
5.2 Interventions and comparators 75
5.3 Acquisition costs 76
5.3.1 EAG critique 77
5.4 Administration costs 78
5.4.1 EAG critique 79
6 Company and EAG cost comparison results 81
6.1 Company base case results 81
6.1.1 Company's scenario analyses 81
6.2 EAG preference assumptions and base case results 82
6.3 Summary statement 82
7 Equalities and innovation 84

8 EAG commentary of the robustness of the evidence submitted by the company 85

9 References 87

10 Appendices 89

10.1 Quality assessment of NADIM-II 89

10.2 Baseline characteristics 90

10.2.1 CheckMate-77T 90

10.2.2 NADIM-II 92

10.2.3 KEYNOTE-671 93

List of Tables

Table 1. Summary of decision problem as outlined in the company submission (Adapted from Table 1 of the CS) 20

Table 2. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal 34

Table 3. Clinical effectiveness studies of technology of interest 37

Table 4. EAG's summary of the design, conduct and analysis of CheckMate-77T 38

Table 5. CheckMate-77T: event-free survival: all randomly assigned patients (ITT population) (Adapted from Table 10 of the CS) 40

Table 6. CheckMate-77T: overall survival—all randomly assigned patients (ITT population) (Reproduced from Table 11 of the CS) 42

Table 7. CheckMate-77T: pathological complete response (per BIPR) and major pathological response (per BIPR)–all randomly assigned patients (ITT population) (Reproduced from Table 12 of the CS) 43

Table 8. CheckMate-77T: objective response rate and best overall response: all randomly assigned patients (ITT population) (Adapted from Table 13 of the CS) 44

Table 9. Subgroup analysis of the CheckMate-77T trial – EFS by BICR (ITT population) (Reproduced from Table 7.2.2.1-1 of CheckMate-77T CSR) 47

Table 10. CheckMate-77T subgroup results for OS by trial stratification factors (Reproduced from company response to clarification question A16) 47

Table 11. EAG's summary of the design, conduct and analysis of KEYNOTE-671 49

Table 12. Subsequent therapies reported in the CheckMate-77T and KEYNOTE-617 trials 50

Table 13. Overview of studies included in the company's updated ITCs. 51

Table 14. EFS Outcome definitions across studies (target population: PD-L1 all-comers stage II-IIIB) (Reproduced from table 8 of the NMA report) 54

Table 15. Traditional Bayesian NMA results for EFS and OS from the company's analyses.....55

Table 16. Event-free survival hazard ratios of perioperative nivolumab versus perioperative pembrolizumab over time in the fractional polynomial network meta-analysis (Adapted from table 17 of the CS and table 18 of the company response to clarification questions).....56

Table 17. Overall survival hazard ratios of perioperative nivolumab versus perioperative pembrolizumab over time in the fractional polynomial network meta-analysis (Adapted from table 18 of the CS and table 19 of the company response to clarification questions).....58

Table 18. Key baseline characteristics across the network of evidence informing the multilevel network meta-regression by study (reproduced from Table 19 of the CS).....59

Table 19. Event-free survival hazard ratios of perioperative nivolumab versus perioperative pembrolizumab over time in the multilevel network meta-regression (adapted from Table 20 of the CS and Table 9 of the company response to clarification questions).....60

Table 20. Overall survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the multilevel network meta-regression (adapted from Table 21 of the CS and Table 12 of the company response to clarification questions).....61

Table 21. Results of Bucher ITCs performed by the EAG comparing perioperative nivolumab with perioperative pembrolizumab 62

Table 22. AEs reported in the CheckMate-77T trial (Reproduced from Table 23 of the CS).....68

Table 23. Most common AEs reported in the CheckMate-77T trial (adapted from Table 8.1.1-1 in the CSR) 69

Table 24. Most common treatment-related AEs reported in the CheckMate-77T and KEYNOTE-671 trials (adapted from Table 8.1.1-1 in the CSR).....70

Table 25. Acquisition costs (adapted from Table 25 in the CS) 76

Table 26. Administration costs (adapted from Table 26 in the CS) 78

Table 27. Sources and values of administration costs.....79

Table 28. Company's base case results.....81

Table 29. Outcomes of scenario analyses 81

Table 30. EAG preferred modelling assumptions 82

Table 31. EAG's base case results 82

Table 32. EAG's summary of the design, conduct and analysis of NADIM-II 89

Table 33. CheckMate-77T: baseline characteristics of patients (Reproduced from Table 6 of the CS) 90

Table 34. NADIM-II: demographic and clinical characteristics of the patients at baseline (ITT population)[a] (Reproduced from Table 8 of the CS) 92

Table 35. KEYNOTE-671: baseline characteristics (Reproduced from Table 10 of the CS appendices) 93

List of Figures

Figure 1. Potential position of perioperative nivolumab in the treatment pathway for resectable NSCLC in clinical practice in England and Wales (Reproduced from CS Figure 3) 17

Figure 2. CheckMate-77T: EFS per BICR, primary definition: all randomly assigned patients (ITT population) (Reproduced from Figure 8 of the CS) 41

Figure 3. CheckMate-77T: overall survival—all randomly assigned patients (ITT population) (Reproduced from Figure 9 of the CS) 42

Figure 4. Point-and-density plot for the comparison of perioperative nivolumab to perioperative pembrolizumab for EFS using the company preferred dataset. 65

Figure 5. Point-and-density plot for the comparison of perioperative nivolumab to perioperative pembrolizumab for EFS-INV. 66

Figure 6. Point-and-density plot for the comparison of perioperative nivolumab to perioperative pembrolizumab for EFS-BICR 2. 66

Figure 7. Point-and-density plot for the comparison of perioperative nivolumab to perioperative pembrolizumab for OS. 67

List of Abbreviations

AE	Adverse events
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
BICR	Blinded independent central review
BIPR	Blinded independent pathology review
BMS	Bristol Myers Squibb
BSA	Body surface area
Chemo	Chemotherapy
CI	Confidence interval
CM77T	CheckMate-77T
CR	Complete response
CTLA-4	Cytotoxic T-Lymphocyte-Associated protein 4
CrI	Credible interval
CS	Company submission
CT	Chemotherapy
DIC	Deviance information criterion
DSU	Decision support unit
EAG	External Assessment Group
ECDF	Empirical cumulative density function
ECOG	Eastern cooperative oncology group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
ESMO	European Society of Medical Oncology
FP-NMA	Fractional polynomial network meta-analysis
GHS	Global Health Status
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
IA	Interim analysis
INV	Investigator-assessed
IPD	Individual patient data
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan Meier
M	Metres
MCID	Minimal clinically important difference
Mg	Milligram

MHRA	Medicines and Healthcare products Regulatory Agency
ML-NMR	Multilevel network meta-regression
MPR	Major pathological response
NA	Not applicable
NCC	National Cost Collection
neoCT	Neoadjuvant chemotherapy
neoNIVO+CT	Neoadjuvant nivolumab plus chemotherapy
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIM	Non-inferiority margin
NIVO	Nivolumab
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
OPROC	Outpatient procedures
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PBO or Pla	Placebo
pCR	Pathological complete response
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PH	Proportional hazards
PS	Performance status
QxW	Every x weeks
R0	Completed resected
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SLR	Systematic literature review
SPC	Summary of Product Characteristics
TKI	Tyrosine kinase inhibitor
TNM	TNM Classification of Malignant Tumors
TTDDM	Time to discontinuation
UK	United Kingdom
UICC	Union for International Cancer Control

1 Executive summary

The company provided a cost-comparison analysis comparing perioperative nivolumab to perioperative pembrolizumab for adults with resectable non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements. The population was narrower than that outlined in the NICE final scope (resectable NSCLC) but aligns with the MHRA marketing authorisation for perioperative nivolumab (adults with resectable [tumours ≥4 cm or node positive] non-small cell lung cancer and no known EGFR mutations or ALK rearrangements). In addition, the intervention was slightly narrower than that detailed in the final scope as perioperative nivolumab is restricted to use with platinum-based chemotherapy in the neoadjuvant period.

The EAG notes that the National Institute for Health and Care Excellence (NICE) guidance states that, "A cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication". Both perioperative pembrolizumab and durvalumab were comparators in the NICE final scope, from which the company considered pembrolizumab to be the most appropriate comparator. Pembrolizumab has the same mode of action as nivolumab and is recommended by NICE for adults with resectable NSCLC with a high risk of recurrence [TA876].

The company presented evidence from two trials (CheckMate-77T and NADIM-II), which compared perioperative nivolumab to placebo. Evidence comparing perioperative pembrolizumab to placebo was presented from the KEYNOTE-671 trial. In the absence of direct comparisons between nivolumab and pembrolizumab, the company used network meta-analyses (NMAs), fractional polynomial NMAs (FP-NMAs) and multilinear network meta-regression (ML-NMR) to perform indirect treatment comparisons (ITCs). The company considered clinical similarity between perioperative nivolumab and perioperative pembrolizumab, and the EAG notes the [redacted] The most common treatment-related adverse events (AEs) were also similar between the two treatments. As a general principle, the EAG has concerns with [redacted]. The EAG notes that the

company's clinical experts expected nivolumab and pembrolizumab to have similar treatment effects, but the EAG considers that ITCs are likely to provide a more robust method to compare the two treatments. In addition, the EAG considers the company's ITCs to be associated with several uncertainties and areas of concern, including:

- The use of different EFS assessment methods from CheckMate-77T and KEYNOTE-671 in the company analysis of EFS;
- The inclusion of NADIM-II in the company's ITCs given its lack of generalisability to clinical practice in England;
- The use of NMA methods that assume proportional hazards (PH) given [redacted];
- The validity of the ML-NMR results due to the EAG's concerns about [redacted];
- The EAG being unable to replicate the company's results including model selection for the FP-NMAs and the ML-NMRs due to time constraints and the lack of the necessary IPD data from the company for the ML-NMR.

The EAG notes the [redacted] perioperative nivolumab and perioperative pembrolizumab for event-free survival (EFS) and overall survival (OS) in the ITCs presented by the company. [redacted]. In addition, given the EAG's concerns about the reliability of the results from the company's ML-NMRs, the EAG considers the results from the FP-NMAs excluding NADIM-II may be the most reliable source of efficacy estimates for perioperative nivolumab versus perioperative pembrolizumab. The EAG notes that in the FP-NMAs excluding NADIM-II for EFS and OS [redacted]

Given the uncertainties outlined above, the EAG is not confident that clinical similarity has been demonstrated between perioperative nivolumab and pembrolizumab. The EAG's conclusion is further supported by [redacted].

In the company's cost comparison analysis, costs relating to adverse events, subsequent treatments, health care resource use and end of life cost were excluded, given the assumption of similar treatment effects between treatments. The company's analysis therefore focuses on the treatment acquisition and administration cost, with both company and EAG base case results finding nivolumab to be cost saving compared to pembrolizumab. However, the reliability of these outcomes is contingent on the assumption of clinical similarity between treatments being valid, which the EAG considers has not been demonstrated with sufficient robustness. The EAG considers it to be beyond the remit of an EAG to consider whether any cost-savings associated with a cost-comparison are sufficiently high to off-set any uncertainty in the analyses of clinical similarity.

2 Background

Lung cancer is the third most common cancer in the United Kingdom (UK) and non-small cell lung cancer (NSCLC) is the most common type of lung cancer.[1] Section B1.3 of the company submission (CS) provides an overview of lung cancer and summarises the symptoms and current clinical pathway for patients with NSCLC in England. The external assessment group (EAG) notes that due to a lack of NSCLC specific UK survival data the company has included some UK survival data for the wider lung cancer population, but the EAG is unclear how relevant this is to the NSCLC population.

The focus of this cost-comparison appraisal is the use of nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable NSCLC. Nivolumab received marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) for use in this indication in February 2025.[2] In addition, nivolumab has a marketing authorisation from the MHRA for use in a variety of other cancers and the company provided a summary of these in Table 2 of the CS. In keeping with the CS, neoadjuvant treatment followed by adjuvant treatment is referred to as "perioperative" treatment throughout this EAG report.

The company has compared perioperative nivolumab to perioperative pembrolizumab, which is already recommended by the National Institute for Health and Care Excellence (NICE) for use as an option for neoadjuvant treatment with platinum-based chemotherapy, then continued alone as adjuvant treatment in adults with resectable NSCLC with a high risk of recurrence [TA1017].[3] The EAG notes that the NICE recommendation for pembrolizumab specifies patients with high risk of recurrence in keeping with its MHRA marketing authorisation. However, the EAG notes that the MHRA marketing authorisation for perioperative nivolumab differs to that of perioperative pembrolizumab in this indication under appraisal, with differences including that nivolumab does not specify patients must be at high risk of recurrence and that nivolumab requires patients to have no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements. The population is discussed in more detail in Section 3.1.

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. This blockade potentiates T-cell antitumour responses. The EAG notes that pembrolizumab has a similar mechanism of action to nivolumab and both drugs are administered using an intravenous (IV) infusion.

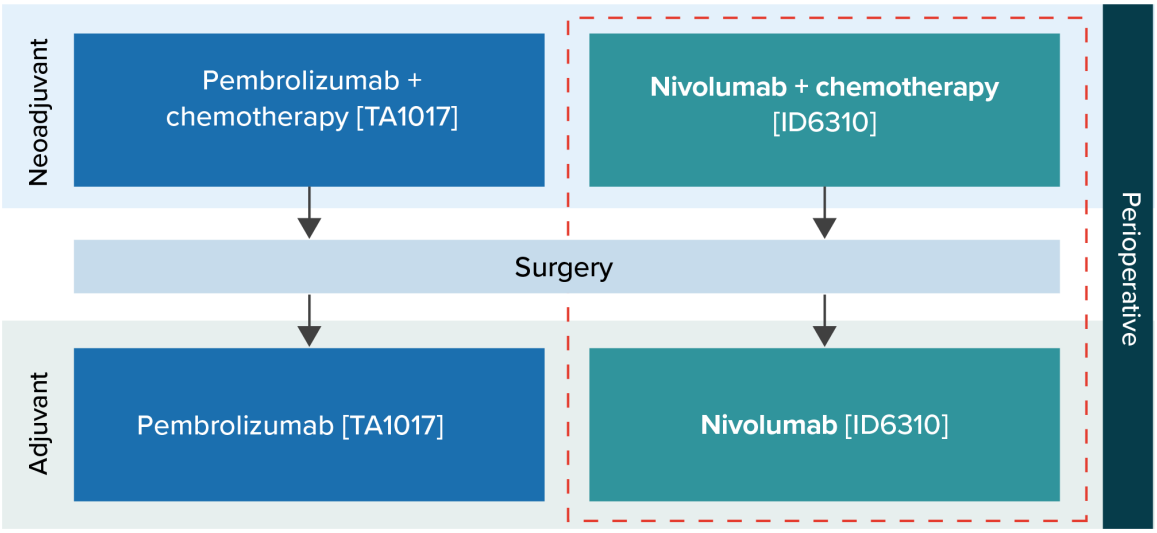
The company provided an overview of the current treatment pathway for NSCLC in the CS (CS Section 1.3.4) along with a summary of the proposed positioning of nivolumab in the treatment pathway (Figure 1). The EAG notes that the company intends for perioperative nivolumab to be positioned as an alternative treatment option to perioperative pembrolizumab. The EAG's clinical experts considered the company's proposed positioning of nivolumab to be reasonable and aligned with its marketing authorisation. The company considers the use of pembrolizumab in this setting to be the current standard of care, but the EAG notes that durvalumab is also available for treatment in a similar positioning.

Durvalumab has a slightly different mechanism of action to nivolumab and pembrolizumab as durvalumab is a human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80. Similar to perioperative nivolumab and pembrolizumab, durvalumab is administered via IV infusion.

Guidance was published in January 2025 by NICE which recommends durvalumab for use as a neoadjuvant treatment with platinum-based chemotherapy, then continued alone as adjuvant treatment, for treating NSCLC in adults whose cancer is resectable (tumours 4 cm or over, or node positive) and has no EGFR mutations or ALK rearrangements [TA1030].[4]

[redacted] The EAG's clinical experts considered durvalumab could potentially be considered a comparator for perioperative nivolumab and the EAG notes that it was included as a comparator in the NICE final scope. The comparators are discussed in more detail in Section 3.3.

Figure 1. Potential position of perioperative nivolumab in the treatment pathway for resectable NSCLC in clinical practice in England and Wales (Reproduced from CS Figure 3)



Abbreviations: NSCLC, non–small cell lung cancer.

Sources: NICE (3); NICE (5)

3 Critique of the decision problem in the company's submission

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE), together with the rationale for any deviation from it, in Section B.1.1 of the company submission (CS).[6] This is summarised in Table 1 below and more detailed comments from the External Assessment Group (EAG) are provided in the subsections that follow.

The EAG has concerns regarding the generalisability to UK clinical practice of one of the trials used to inform perioperative nivolumab in the company's indirect treatment comparisons (ITCs; [NADIM-II; Section 3.1 and 3.2]).[7] In addition, the EAG notes that not all outcomes specified in the NICE final scope were included in the ITCs for perioperative nivolumab versus perioperative pembrolizumab (Section 3.4) and that the subgroups detailed in the NICE final scope were not explicitly covered in the CS.

Table 1. Summary of decision problem as outlined in the company submission (Adapted from Table 1 of the CS)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG critique
Population	People with resectable non–small cell lung cancer (NSCLC)	People with resectable NSCLC	NA	The EAG notes that the MHRA marketing authorisation for perioperative nivolumab is narrower than the population specified in the NICE final scope as the MHRA marketing authorisation restricts the use of perioperative nivolumab to adults with resectable (tumours ≥4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements. However, the population in the CheckMate-77T trial is consistent with the company's proposed positioning of perioperative nivolumab and its marketing authorisation (see Section 3.1 for further details). The EAG has concerns that the population in the NADIM-II clinical trial is narrower than that of CheckMate-77T and that it is not fully representative of the population with NSCLC in England, e.g. in terms of disease stage as only Stage IIIa and IIIb patients were included and no stage II patients were included (see Section 3.1 for further details).
Intervention	Nivolumab with chemotherapy for neoadjuvant treatment then nivolumab monotherapy for adjuvant treatment	Nivolumab with chemotherapy for neoadjuvant treatment then nivolumab monotherapy for adjuvant treatment	NA	The EAG notes that the nivolumab regimens used in CheckMate-77T were consistent with the MHRA marketing authorisation. The EAG also notes that the perioperative nivolumab marketing authorisation specifies platinum-based chemotherapy which is also consistent with the CheckMate-77T trial. The chemotherapy regimens used in the trial were deemed broadly reflective of clinical practice in England by the EAGs clinical advisers. The EAG notes that the nivolumab duration in the neoadjuvant and adjuvant settings of NADIM-II were

				shorter than that specified in the MHRA marketing authorisation. The EAG is thus concerned about the generalisability and applicability of the results from NADIM-II to clinical practice in England. See Section 3.2 for further details.
Comparator(s)	• Neoadjuvant pembrolizumab (with chemotherapy) then adjuvant pembrolizumab monotherapy • Neoadjuvant durvalumab (with chemotherapy) then adjuvant durvalumab monotherapy	Neoadjuvant pembrolizumab (with chemotherapy) then adjuvant pembrolizumab monotherapy	The company considers pembrolizumab to be the new SOC treatment for patients with resectable NSCLC in England, and thus believes that the most relevant comparator for cost comparison decision-making is perioperative pembrolizumab, for the following reasons: • [redacted] Nivolumab and pembrolizumab have the same mechanism of action—both are PD-1 inhibitors, whereas durvalumab is a PD-L1 inhibitor. • The company stated that an indirect treatment comparison of nivolumab and pembrolizumab demonstrates a similar EFS and OS treatment effect between nivolumab and pembrolizumab, which supports the similarity in clinical trial results for perioperative nivolumab (CheckMate-77T) and perioperative pembrolizumab	The company has selected perioperative pembrolizumab as the comparator for perioperative nivolumab in this cost comparison evaluation, and based on the advice from clinical experts, the EAG considers the company's choice of pembrolizumab to be reasonable (See Section 3.3 for further details). The EAG notes that there is no head-to-head data available for perioperative nivolumab versus perioperative pembrolizumab and therefore the company has conducted indirect treatment comparisons using a variety of different methods (Section 4.4). In addition, in the company response to clarification questions, the company has conducted indirect treatment comparisons for perioperative nivolumab versus perioperative durvalumab, and these are summarised in Section 4.4.

			(KEYNOTE-671) (See Section B.3.8 and Appendix D of the company submission.)	
Outcomes	The outcome measures to be considered include: • EFS • pCR • Response rates • OS • Adverse effects of treatment • Health-related quality of life	The outcome measures considered include: • EFS • pCR • Response rates • OS • Adverse effects of treatment • Health-related quality of life	NA	Data on all of the outcomes specified in the NICE final scope were reported in the CS for perioperative nivolumab with data available from CheckMate-77T. In addition, data were provided from NADIM-II for pCR, OS and PFS. For the ITCs of perioperative nivolumab versus perioperative pembrolizumab, data were only reported for EFS and OS. The EAG is concerned that the company's analyses of EFS use different methods of assessment for nivolumab and pembrolizumab (investigator-assessed and BICR) therefore, additional analyses were requested during clarification. See Section 3.4 for further details.
Economic analysis	This technology has been selected to be appraised as a cost comparison. The reference case stipulates that the time	BMS present a cost comparison analysis comparing the drug and administration costs of	NA	Costs considered in the company's cost comparison analysis are of an NHS and Personal Social Services perspective with the time horizon reflecting a full course of treatment. Under the assumption of treatment effects being similar, the focus of the analysis on acquisition and administration costs is appropriate.

	horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	perioperative nivolumab versus perioperative pembrolizumab for a full course of treatment. All other costs are anticipated to be the same.		

Subgroups to be considered	If the evidence allows, subgroups will be considered based on: • Whether nivolumab is used before and after surgery • PD-L1 tumour proportion score • Disease stage • Presence of biological or genetic markers • Histology (squamous vs. non-squamous)	BMS do not explore subgroup analyses for in this submission.	BMS seek reimbursement for the ITT population of the CheckMate-77T trial in line with the MHRA licence[2] and in line with TA1017[3] reimbursement. A significant patient benefit was observed in the primary analysis population of the CheckMate-77T trial, with a statistically significant and clinically relevant improvement in EFS compared with chemotherapy alone (HR, [redacted] 95% CI, [redacted].[9]	The EAG notes that the following were prespecified subgroup analyses in CheckMate-77T, and stratification factors at randomisation, with results for EFS and OS provided by the company in response to clarification or available from the CSR: • Tumour histology (squamous/non-squamous); • NSCLC stage (II vs. III); • PD-L1 status (≥ 1%/< 1%, indeterminate, or not evaluable). Subgroup analyses based on whether nivolumab is used before and after surgery, and presence of biological or genetic markers were not reported in the CS or CSR for CheckMate-77T. The EAG also notes that the MHRA marketing authorisation restricts the use of perioperative nivolumab to patients with no known EGFR mutations or ALK rearrangements.
Special considerations, including issues related to	Guidance will only be issued in accordance with the marketing authorisation. Where the	There are no anticipated equity or equality issues associated	NA	NA

equity or equality	wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	with this appraisal.		

Abbreviations: ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; EAG, evidence assessment group; EFS, event-free survival; EGFR, epidermal growth factor receptor; ITC, indirect treatment comparison; ITT, intention to treat; MHRA, Medicines and Healthcare Products Regulatory Agency; NA, not applicable; NHS, National Health Service; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death-ligand 1; SOC, standard of care

3.1 Population

Clinical effectiveness data for neoadjuvant nivolumab + chemotherapy followed by adjuvant nivolumab (perioperative nivolumab) in CS are derived from the CheckMate-77T and NADIM-II trials which were designed to evaluate the efficacy and safety of neoadjuvant nivolumab + chemotherapy followed by adjuvant nivolumab, compared with neoadjuvant placebo + chemotherapy followed by adjuvant placebo. Patients eligible for inclusion in CheckMate-77T were those with newly diagnosed resectable stage IIA (> 4 cm) to stage IIIB (T3N2 or T4N2; according to the American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) 8th edition[10]) non-small-cell lung cancer (NSCLC). The NADIM-II trial restricted enrolment of patients to those with previously untreated resectable (according to the AJCC/UICC 8th edition) stage IIIA or IIIB NSCLC and thus excluded patients with stage II disease.

The final scope issued by NICE specifies the population of interest to be people with resectable NSCLC but the MHRA marketing authorisation wording for perioperative nivolumab restricts it use to adults with resectable (tumours ≥4 cm or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements. The EAG notes that the marketing authorisation does not specify disease stage but based on advice from clinical experts, the EAG considers the population in CheckMate-77T to be broadly consistent with that of the MHRA marketing authorisation and the patients in whom they would anticipate using perioperative nivolumab in clinical practice in England. The EAG notes that both CheckMate-77T and NADIM-II excluded patients with known EGFR mutations or ALK translocations, but the EAG also notes that in CheckMate-77T only nonsquamous tumours that had unknown EGFR mutation status were to be tested for EGFR mutations. Furthermore, ALK testing was not formally specified in the trial protocol. The EAG thus considers there are potentially some patients with undiagnosed EGFR mutations and/or ALK rearrangements included in the CheckMate-77T trial population. The EAG notes from its clinical experts that EGFR mutations or ALK rearrangements would generally be expected to be diagnosed prior to commencing perioperative nivolumab in clinical practice in England, as patients with these would generally follow a different treatment pathway.

The EAG notes that the population specified in the MHRA marketing authorisation for the use of perioperative pembrolizumab is adults with resectable NSCLC at high risk of recurrence.[11] The criteria for defining patients with high risk of recurrence include patients with Stage II – IIIB (N2) NSCLC according to the 8th edition staging system with: tumour size > 4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that invade thoracic structures; or

tumours that involve a mainstem bronchus with tumour > 4 cm; or tumours > 4 cm that cause obstructive atelectasis that extends to the hilum; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary lung cancer. The EAG notes that the MHRA marketing authorisation does not restrict the use of perioperative nivolumab to patients at high risk of recurrence but the EAG's clinical experts considered the population in which they would expect to use perioperative nivolumab would be similar to that where perioperative pembrolizumab is approved and currently used.

The EAG also notes that the MHRA marketing authorisation and NICE recommendation for perioperative durvalumab is similar to the MHRA marketing authorisation for perioperative nivolumab (durvalumab is recommended in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab monotherapy after surgery, for the treatment of adults with resectable[tumours ≥ 4 cm and/or node positive] NSCLC and no known EGFR mutations or ALK rearrangements).[4, 12] The EAGs clinical experts reported that the CheckMate-77T population was slightly younger, had slightly more patients with ECOG performance status 0, fewer patients with nonsquamous cell carcinomas and more patients on neoadjuvant cisplatin than expected in clinical practice in England.

The study used to inform perioperative pembrolizumab in the indirect treatment comparisons (ITCs) in the CS was KEYNOTE-671. The EAGs clinical experts reported that the population in KEYNOTE-671 had a slightly younger median age and a slighter better ECOG performance status than expected in clinical practice in England but the proportion with nonsquamous cell carcinoma more closely reflected clinical practice. The EAG notes that a small proportion of patients with known ALK rearrangements (3%) and/or known EGFR mutations (4%) were included in KEYNOTE-671 with over 60% of patients having unknown ALK status and a similar number with unknown EGFR status.

In summary, the EAG considers the population covered in the CS to be appropriate and that the population in the CheckMate-77T more accurately reflects the expected population to be treated in clinical practice in England than NADIM-II in terms of disease stage. The EAG also notes that the population in CheckMate-77T and in the MHRA marketing authorisation for perioperative nivolumab is narrower compared to the population detailed in the NICE final scope as they restrict the use of perioperative nivolumab to adults with resectable (tumours ≥4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.

3.2 Intervention

The intervention specified in the NICE final scope was nivolumab with chemotherapy for neoadjuvant treatment then nivolumab monotherapy for adjuvant treatment and the intervention in the CS is slightly narrower but aligned with the MHRA marketing authorisation which specifies that the chemotherapy regimen in the neoadjuvant stage should be platinum-based. The EAG notes that nivolumab received marketing authorisation from the MHRA in February 2025 for use in combination with platinum-based chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment after surgical resection.[2] This was indicated for the treatment of adults with resectable (tumours ≥4 cm or node positive) non-small cell lung cancer and no known EGFR mutations or ALK rearrangements.

The MHRA recommended dose of nivolumab in the neoadjuvant phase is 360 mg administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for up to 4 cycles or until disease progression or unacceptable toxicity. Following surgery, the recommended dose of nivolumab for the adjuvant phase is 480 mg every 4 weeks as monotherapy for up to 13 cycles or until disease recurrence or unacceptable toxicity. The EAG notes that this treatment regimen is consistent with that used in the CheckMate-77T trial, but a different regimen was used in the NADIM-II trial. In NADIM-II, the same doses of nivolumab were used but neoadjuvant treatment was only given for up to 3 cycles and adjuvant treatment was only given for up to 6 months rather than 1 year. The EAG notes that in CheckMate-77T all four neoadjuvant nivolumab treatment cycles were completed in the majority of patients (84.7% in the perioperative nivolumab arm and 88.4% in the chemotherapy arm) and only 3.9% of patients in CheckMate-77T received just three cycles of neoadjuvant therapy.[13] The EAG is therefore particularly concerned that there is a discrepancy in the neoadjuvant treatment duration between NADIM-II and CheckMate-77T and is unsure what impact this may have on the overall trial results.

The chemotherapy regimens used in the neoadjuvant periods in both CheckMate-77T and NADIM-II were platinum-based regimens, in keeping with the MHRA marketing authorisation. In CheckMate-77T, patients received platinum-doublet chemotherapy based on tumour histology. Patients with squamous cell carcinomas received cisplatin (75 mg/m^2) plus docetaxel (75 mg/m^2) or carboplatin (area under the concentration–time curve [AUC] 5 or 6) plus paclitaxel (175 or 200 mg/m^2). Patients with nonsquamous cell carcinomas received cisplatin (75 mg/m^2) plus pemetrexed (500 mg/m^2), carboplatin (AUC 5 or 6) plus pemetrexed (500 mg/m^2), or carboplatin (AUC 5 or 6) plus paclitaxel (175 or 200 mg/m^2). In NADIM-II the chemotherapy regimen for all patients was paclitaxel (200 mg/m^2 of body-surface area), and carboplatin (AUC 5). The EAGs clinical experts considered the

chemotherapy treatment regimens used in CheckMate-77T and NADIM-II to be reasonable and broadly consistent with clinical practice in England but highlighted that carboplatin is generally used more frequently used than cisplatin. One of the clinical experts noted that pemetrexed is not routinely used for early-stage NSCLC and is instead used more frequently for patients with stage IV disease. Nonetheless, the EAGs clinical experts reported that they would not expect treatment efficacy to differ substantially between the different chemotherapy regimens used in the two trials.

In summary, the EAG considers the perioperative nivolumab treatment regimen used in CheckMate-77T to be broadly consistent with the expected use of perioperative nivolumab in clinical practice in England and the notes that perioperative nivolumab is restricted to use with platinum-based chemotherapy in the neoadjuvant period. The EAG is concerned that the treatment regimen in terms of the number of cycles of nivolumab in NADIM-II does not reflect the MHRA recommendation for perioperative nivolumab.

3.3 Comparators

The comparators specified in the NICE final scope were:

- Neoadjuvant durvalumab (with chemotherapy) then adjuvant durvalumab monotherapy; and
- Neoadjuvant pembrolizumab (with chemotherapy) then adjuvant pembrolizumab monotherapy.

The company reported that pembrolizumab is the new standard of care treatment for patients with resectable NSCLC in England, and thus they considered it to be the most relevant comparator for this cost comparison evaluation is perioperative pembrolizumab. The company provided further justification for their choice of comparator, including that:

- [redacted]Niv

olumab and pembrolizumab have the same mechanism of action as PD-1 inhibitors, whereas durvalumab is a PD-L1 inhibitor.

- The company stated that an indirect treatment comparison of nivolumab and pembrolizumab demonstrates a similar event-free survival (EFS) and overall survival (OS) treatment effect between nivolumab and pembrolizumab, which the company considered to support the similarity in clinical trial results for perioperative nivolumab (CheckMate-77T) and perioperative pembrolizumab (KEYNOTE-671).

The EAG notes that NICE guidance recommending pembrolizumab as an option for neoadjuvant treatment with platinum-based chemotherapy, then continued alone as adjuvant treatment, for resectable non-small-cell lung cancer (NSCLC) with a high risk of recurrence in adults was published in November 2024. In January 2025, following comparisons against neoadjuvant nivolumab, guidance was published by NICE recommending durvalumab for use as a neoadjuvant treatment with platinum-based chemotherapy, then continued alone as adjuvant treatment, for treating NSCLC in adults whose cancer is resectable (tumours 4 cm or over, or node positive) and has no EGFR mutations or ALK rearrangements [TA1030].[4] Based on the advice of clinical experts, the EAG notes that both perioperative pembrolizumab and perioperative durvalumab could be considered comparators for perioperative nivolumab. In addition, the advice from the EAG's clinical experts [redacted]

The company uses clinical evidence from the KEYNOTE-671 trial of perioperative pembrolizumab versus neoadjuvant chemotherapy and placebo in indirect treatment comparisons (ITCs) to compare against perioperative nivolumab due to a lack of head-to head trial data. Pembrolizumab was given at a dose of 200 mg intravenously once every 3 weeks for up to 4 cycles in the neoadjuvant phase of KEYNOTE-671. Patients also received neoadjuvant chemotherapy every 3 weeks for up to 4 cycles with cisplatin (75 mg/m^2) and gemcitabine (1,000 mg/m^2 on days 1 and 8 of the 3-week cycles) in patients with squamous histologic features or cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) in those with non-squamous histologic features. The EAG notes that the company's clinical experts

expected nivolumab and pembrolizumab to have similar treatment effects, but the EAG considers that ITCs are likely to provide a more robust method to compare the two treatments.

The EAG notes that whilst the chemotherapy regimen used in KEYNOTE-671 for patients with nonsquamous histology was an option in CheckMate-77T, the gemcitabine part of the regimen used for patients with squamous histology was not available in CheckMate-77T. The EAG also notes from its clinical experts that carboplatin tends to be used more frequently than cisplatin for this indication in clinical practice in England although clinical experts reported that efficacy would not be expected to differ substantially between the chemotherapy regimens used in KEYNOTE-671 and those used in clinical practice in England.

Following surgery, treatment in the adjuvant phase of KEYNOTE-671 comprised of pembrolizumab monotherapy at a dose of 200 mg intravenously once every 3 weeks for up to 13 cycles. The MHRA marketing authorisation for pembrolizumab in this indication also permits the use of 6 weekly 400 mg pembrolizumab as an alternative to the 3 weekly 200 mg pembrolizumab treatment regimen in both the neoadjuvant (2 doses of 400 mg of pembrolizumab every 6 weeks in combination with chemotherapy) and adjuvant treatment phases (7 doses of 400 mg of pembrolizumab every 6 weeks). The EAG's clinical experts reported that generally the 3 weekly pembrolizumab regimen is used in the neoadjuvant phase and the 6 weekly regimen is considered for the later adjuvant phase treatments. The EAG notes that in TA1030, the pembrolizumab regimen used in the company's economic model was based on expert advice and includes the assumption that patients in the adjuvant setting receive 1 cycle of pembrolizumab 200 mg followed by a maximum of 6 cycles of 400 mg of pembrolizumab every six weeks (Q6W). The EAG considers it to be unclear whether the difference in pembrolizumab dosing regimens between KEYNOTE-671 and expected clinical practice in England would result in any difference in efficacy.

Based on the advice from clinical experts, the EAG considers the company's selection of perioperative pembrolizumab as the key comparator for perioperative nivolumab to be reasonable. In addition, the EAG considers the KEYNOTE-671 trial to be reasonable for informing perioperative pembrolizumab in the ITCs compared to nivolumab, although the dosing regimen in KEYNOTE-671 may not be consistent with that used in clinical practice in England.

3.4 Outcomes

The outcomes specified in the NICE final scope are:

- event-free survival (EFS);

- pathological complete response;
- response rates;
- overall survival (OS);
- adverse effects of treatment;
- health-related quality of life (HRQL).

The EAG notes that the company has provided clinical data from CheckMate-77T for all the outcomes specified in the NICE final scope. Furthermore, event-free survival, which was assessed in a time-to-event analysis from randomisation to disease progression or death from any cause evaluated by blinded independent central review (BICR) according to the Response Evaluation Criteria in Solid Tumors (version 1.1), was the primary efficacy outcome in CheckMate-77T. Results for EFS as assessed by investigator in CheckMate-77T were provided in the company's response to clarification questions. The EAG also notes that limited data on HRQL outcomes were presented in the CS with results reported focusing on the EQ-5D-3L VAS scores from CheckMate-77T, but additional results were provided in the CheckMate-77T clinical study report. In addition, the company included results from some exploratory endpoints in CheckMate-77T in the CS that were not requested in the NICE final scope e.g. time to death or distant metastases per investigator and EFS on next line of therapy per investigator. The EAG focuses its critique on the outcomes requested in the NICE final scope and notes that in TA1017 the key efficacy outcome of relevance for the economic model from the company's network meta-analyses was EFS.[3]

Efficacy data from NADIM-II were more limited compared to that from CheckMate-77T, with data in the CS limited to pathological complete response (primary endpoint), progression-free survival and OS.

The EAG notes that the company ITCs only considered the outcomes of EFS and OS, which the EAG considers to be reasonable. TTD differences between treatments were not assessed by the company as TTD data for pembrolizumab from KEYNOTE-671 was not available. In addition, the EAG's clinical experts reported that they would not expect any major differences in serious adverse effects between nivolumab, pembrolizumab and durvalumab.

Based on advice from clinical experts, the EAG considers that the outcomes presented in the CS are clinically relevant to the decision and address the NICE final scope.

4 Summary of the EAG's critique of clinical effectiveness evidence submitted

4.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trials (RCTs) that compared the efficacy and safety of nivolumab or comparators in patients with resectable NSCLC. The EAG considers the SLR methods used by the company to be appropriate, although notes that the SLR was last updated in 2024 so could potentially have missed more recent evidence. Table 2 contains the EAG's assessment of the company's methods used for the SLR, with full details reported in Appendix D of the CS.

Table 2. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	CS Appendix D, Section D.1.1	**Appropriate** The following databases were searched: • MEDLINE • Embase • Central Register of Controlled Trials (CENTRAL) Conference proceedings in Embase were searched for the two years prior to the date of the search.
Search strategies	CS Appendix D, Section D.1.1.1	**Appropriate strategy. Some concerns about search dates** Searches were appropriate for the decision problem and included the relevant population, intervention, comparator and study designs. The initial search was performed in March 2019, followed by update searches which were last performed in November 2024. This was ten months prior to the company's submission, and it is therefore possible that the SLR could have missed more recent, relevant, references. The main trial in the CS (CheckMate-77T) was identified in the SLR.
Inclusion criteria	CS Appendix D, Section D.1.1.2	**Appropriate** The population, intervention and comparators match those in the NICE final scope and decision problem. Outcomes were appropriate to meet those specified in the scope. The SLR appears unlikely to have missed any relevant studies based on the inclusion criteria.
Screening	CS Appendix D, Section D.1.1.2	**Appropriate** Abstract and full-text screening was completed by two independent investigators, with discrepancies resolved by a third reviewer.

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data extraction	CS Appendix D, Section D.1.1.3	**Appropriate** Data was extracted by a single reviewer in customised data extraction forms. Key information was validated by a second reviewer.
Tool for quality assessment of included study or studies	CS Appendix D, Section D.1.1.4 and D.1.2.6 CS, Section B.3.4	**Some concerns** Study quality was assessed using the minimum criteria for assessing risk of bias, as recommended in the NICE "Single technology appraisal: User guide for company evidence submission template". However, explanations for the quality judgement for each domain were not provided.

Abbreviations: CS, company submission; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; SLR, systematic literature review

The SLR identified 15,337 records in the search from November 2024. Out of those, 12,739 were included for abstract screening following de-duplication (Figure 1, CS Appendix D). A total of 155 full-text articles were screened, with 13 identified as relevant. Of these, ten included interventions other than perioperative nivolumab or pembrolizumab and were therefore excluded, leaving three publications meeting the criteria for inclusion in the company's ITCs. Of these, two were phase III RCTs and one was a phase II RCT which assessed the following interventions:

- Neoadjuvant nivolumab and chemotherapy, followed by adjuvant nivolumab:
  - CheckMate-77T (Phase III RCT);[13]
  - NADIM-II (Phase II RCT).[7]
- Neoadjuvant pembrolizumab and chemotherapy, followed by adjuvant pembrolizumab:
  - KEYNOTE-671 (Phase III RCT).[14]

All three studies were included in the company's indirect treatment comparisons (ITCs). The EAG notes that the ITCs reported in the CS were conducted using a restricted network of trials from a wider network, that included additional studies reporting on treatments outside the NICE final scope. Further details about the studies included in the ITCs (CheckMate-77T, NADIM-II and KEYNOTE-671) and the methods of the ITCs are provided in Section 4.4.

While all three included studies reported on relevant interventions, the EAG had concerns about the relevance of NADIM-II to clinical practice. At clarification, the EAG, therefore, requested updated ITC analyses which excluded the results of the NADIM-II trial. More details about the EAG's concerns

around the NADIM-II trial, and the impact of removing the trial from the ITCs are provided in Sections 4.2 to 4.5.

4.2 Critique of trials of the technology of interest

Two RCTs (CheckMate-77T[13] and NADIM-II[7]), both comparing neoadjuvant nivolumab and chemotherapy, followed by adjuvant nivolumab (perioperative nivolumab) to neoadjuvant chemotherapy (with placebo), were the focus of this submission. The key information for both trials is summarised in Table 3.

The EAG notes that CheckMate-77T is a phase III trial that was funded by the company (Bristol Myers Squibb) and was used to inform the MHRA marketing authorisation for the use of nivolumab in the indication of relevance to this cost comparison evaluation. NADIM-II is a phase II trial that was funded by both the company and additional grants. The latter trial was not used to inform the MHRA marketing authorisation for nivolumab. The EAG also notes that NADIM-II was conducted solely in centres in Spain; the population enrolled is narrower compared to that in CheckMate-77T; and the permitted nivolumab treatment regimen does not align with that in CheckMate-77T or the MHRA marketing authorisation. The EAG is therefore concerned about the generalisability of the evidence from NADIM-II to clinical practice in England. Although CheckMate-77T was also not conducted in the UK, the other concerns associated with NADIM-II do not apply, and the EAG's clinical experts considered the population and treatments in CheckMate-77T to be applicable to NHS clinical practice. The EAG therefore considers the key nivolumab trial of relevance to this cost comparison evaluation to be CheckMate-77T. As a result, it has focused its critique on CheckMate-77T but also summarised the results from NADIM-II.

The EAG's assessment of the trial design and analysis methods for CheckMate-77T is presented in Table 4. An assessment of the trial design and analysis methods for NADIM-II is presented in Appendix 10.1 (Table 32).

Table 3. Clinical effectiveness studies of technology of interest

	CheckMate-77T	NADIM-II
Role in this evaluation	Used as a key source of clinical effectiveness evidence. Included in the CS as a direct comparison with placebo and in the indirect treatment comparisons to help inform the company's primary comparisons between nivolumab and pembrolizumab.	Used as a key source of clinical effectiveness evidence. Included in the CS as a direct comparison with placebo and in the indirect treatment comparisons to help inform the company's primary analysis of nivolumab versus pembrolizumab. Due to concerns around the study's generalisability to NHS clinical practice, the EAG's preferred analyses exclude NADIM-II from the ITCs.
Study type	Phase III, randomised, double-blind trial	Phase II, randomised, open-label trial
Patient group	Patients with newly diagnosed resectable (stage IIA [> 4 cm] to stage IIIB [T3N2 or T4N2]), AJCC/UICC 8th edition) NSCLC	Patients with resectable (according to the AJCC/UICC 8th edition) stage IIIA or IIIB NSCLC
Subgroups	Pre-planned subgroups: • Tumour histology (squamous/non-squamous) • NSCLC stage (II vs. III) • PD-L1 status (≥ 1%/< 1%, indeterminate, or not evaluable)	None reported in CS
Exclusion criteria	Key exclusion criteria. Patients with: • prior chemotherapy or any other cancer therapy for resectable NSCLC • an active, known or suspected autoimmune disease • known EGFR mutations or ALK translocations • grade ≥ 2 peripheral neuropathy • brain metastases • a condition requiring systemic treatment with immunosuppressive medications within 14 days of randomisation • interstitial lung disease or active, non-infectious pneumonitis • previous malignancies unless a complete remission ≥ 2 years prior to first treatment and no additional therapy required • a history of allergy or hypersensitivity to study drugs and their components	Key exclusion criteria. Patients with: • known EGFR mutations or ALK translocations • active, known or suspected autoimmune disease • a condition requiring systemic treatment with corticosteroids or immunosuppressive medications within 14 days of randomisation • a history of ILD if they have symptomatic ILD (grade 3-4) and/or poor lung function • an active, known or suspected autoimmune disease • previous malignancies unless a complete remission ≥ 2 years prior to first treatment and no additional therapy required • prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2 or anti–CTLA-4 antibody

	CheckMate-77T	NADIM-II
Intervention	Nivolumab 360 mg administered as an intravenous injection every 3 weeks + standard of care chemotherapyfor up to 4 cycles as neoadjuvant treatment followed by surgery, and then nivolumab monotherapy 480 mg administered as an intravenous injection every 4 weeks for up to 13 cycles (approximately 1 year) as adjuvant therapy after surgery	Nivolumab 360 mg administered as an intravenous injection plus chemotherapy (paclitaxel 200 mg/m^2 BSA and carboplatin AUC 5 mg/mm/min) as neoadjuvant treatment every 3 weeks up to 3 cycles, followed by surgery; for patients with R0 resections only, nivolumab monotherapy 480 mg once every 4 weeks for 6 months as adjuvant therapy after surgery
Comparator	Placebo administered as an intravenous injection every 3 weeks + standard of care chemotherapyfor up to 4 cycles as neoadjuvant therapy, followed by surgery, and then placebo every 4 weeks for up to 13 cycles (approximately 1 year) after surgery	Chemotherapy (paclitaxel 200 mg/m^2 BSA and carboplatin AUC 5 mg/mm/min) as neoadjuvant treatment every 3 weeks up to 3 cycles, followed by surgery, and then 3 observation visits after surgery
Duration	Median follow-up: [redacted]	Median follow-up: 26.1 months
Location	86 sites in 18 countries (Argentina, Australia, Belgium, Brazil, China, Czech Republic, France, Germany, Italy, Japan, Mexico, Netherlands, Poland, Romania, Russian Federation, Spain, Taiwan, the United States)	21 sites in Spain

Abbreviations: AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control; ALK, anaplastic lymphoma kinase; BSA, body surface area; CS, company submission; CTLA-4, Cytotoxic T-Lymphocyte-Associated protein 4; EAG, evidence assessment group; EGFR, Epidermal Growth Factor Receptor; ITC, indirect treatment comparison; NHS, National Health Service; NMA, network meta-analysis; NSCLC, non-small cell lung cancer

Table 4. EAG's summary of the design, conduct and analysis of CheckMate-77T

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	CM77T Protocol - Section 5.1	**Appropriate** Patients were randomised using 1:1 randomisation using the IRT. Patients were stratified by tumour histology, NSCLC stage and PD-L1 status.
Concealment of treatment allocation	CM77T Protocol - Section 7.3	**Appropriate** The study was double-blind, with access to treatment allocation only available through the IRT to an unblinded pharmacist or other individual who was responsible for dispensing the blinded treatment but not involved in any other aspect of the study.
Eligibility criteria	CS – Section B.3.3.1, Table 5	**Appropriate** • Males and females aged ≥ 18 years • Histologically confirmed stage IIA > 4 cm) to IIIB (T3N2 or T4N2) non–small cell lung cancer (NSCLC) (according to

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
		AJCC 8th edition) with disease that is considered resectable • Eligible for complete resection and must agree to undergo SOC surgery for complete resection of NSCLC after neoadjuvant therapy • No prior systemic anticancer treatment for NSCLC • ECOG PS of 0-1 • Tissue from lung tumour to be available for biomarker testing
Baseline characteristics	CS – Section B.3.3.1.1, Table 6	**Appropriate** There were some differences between trial arms, such as race, smoking status and previous chemotherapy, but the EAG's clinical experts did not consider these a major concern. They highlighted how patients with higher PD-L1 expression can have a better response to immunotherapy but did not think the difference between trial arms was sufficient to have a meaningful impact on the results.
Dropouts	CS – Section B.3.3.1.1, Figure 5	**Appropriate** Dropouts were relatively low and similar across trial arms.
Statistical analysis		
Sample size and power	CS – Section B.3.2 -Table 4	**Appropriate** The study was designed to have >90% power to detect a HR of 0.65 with a two-sided type I error of 0.05, according to the observation of approximately 231 patients with disease progression or recurrence, abandoned surgery, or death. The planned sample size was 452 and a total of 461 patients were randomised to study treatments.
Handling of missing data	Not applicable	**Unclear** The company has not provided any information on how missing data were handled; therefore, it is unclear to the EAG if this was done appropriately.
Outcome assessment	CS – Section B.3.2 -Table 4	**Appropriate** Clinical response outcomes were assessed using measures that are commonly used in practice or research. The EAG's clinical experts noted that HRQoL is not commonly formally assessed in NHS clinical practice for NSCLC.

Abbreviations: AJCC, American Joint Committee on Cancer; EAG, External Assessment Group; IRT, interactive response technology; NSCLC, non-small cell lung cancer

4.3 Clinical effectiveness results

4.3.1 CheckMate-77T

The results for event-free survival (EFS), overall survival (OS) and the safety analyses presented in the CS were reported using a database lock from 16 December 2024 with a median follow-up of [redacted] The results for the remaining efficacy outcomes specified in the NICE final scope were reported in the CS using data from the first interim analysis of CheckMate-77T which had a database lock of 6 September 2023 with a median follow-up of 25.4 months. The EAG notes that the 16 December 2024 was the first planned interim analysis of OS and that it was reported to be the most recent analysis of EFS. The EAG considers that the most recent data-cut is the most relevant source of data and notes that only EFS and OS are used in the company's indirect treatment comparisons (ITCs).

4.3.1.1 EFS

Event-free survival (EFS) in CheckMate-77T was defined as the 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.

EFS assessed by blinded independent central review (EFS-BICR) was the primary outcome in CheckMate-77T and at the 16 December 2024 database lock, median EFS-BICR was [redacted] in the nivolumab group ([redacted], 95% confidence interval [CI]: [redacted]) compared to in the chemotherapy group ([redacted], 95% CI: [redacted]) with a hazard ratio (HR) of [redacted] (95% CI: [redacted]) (Table 5, Figure 2). The EAG also notes that the results for investigator-assessed EFS (EFS-INV) [redacted] and the HR for EFS-INV was [redacted] (Table 5).

Table 5. CheckMate-77T: event-free survival: all randomly assigned patients (ITT population) (Adapted from Table 10 of the CS)

Events, n (%) for EFS-BICR	[redacted]	[redacted]
Events, n (%) for EFS-INV[b]	[redacted]	[redacted]
Median EFS-BICR (95% CI, months)[a]	[redacted]	[redacted]
Median EFS-INV (95% CI, months)[b]	[redacted]	[redacted]

HR (95% CI) for EFS-BICR	[redacted]		
HR (95% CI) for EFS-INV[b]	[redacted]		
24 months EFS-BICR, %[c]	[redacted]		[redacted]
30 months EFS-BICR, %[c]	[redacted]		[redacted]

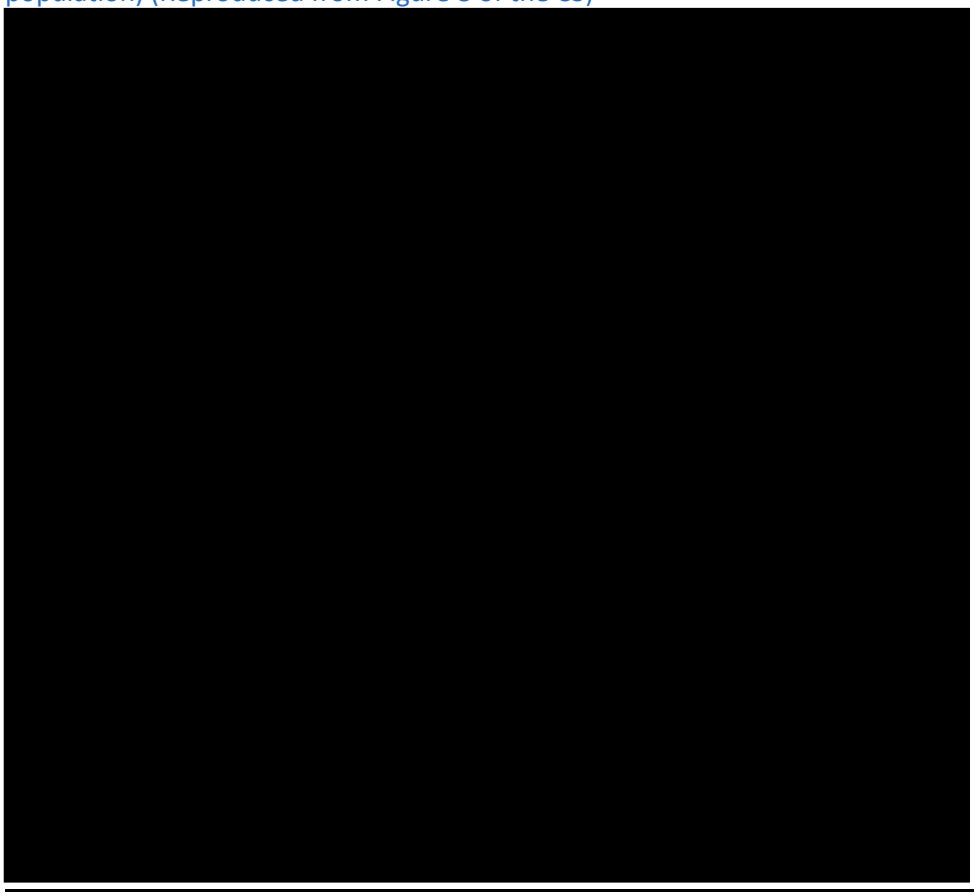
Abbreviations: BICR, blinded independent central review; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intention to treat; INV, investigator-assessed; NR, not reached.

[a] Based on Kaplan-Meier estimates.

[b] Data from company response to clarification question A10

[c] Data not available for EFS-INV

Figure 2. CheckMate-77T: EFS per BICR, primary definition: all randomly assigned patients (ITT population) (Reproduced from Figure 8 of the CS)



Abbreviations: BICR, blinded independent central review; Chemo, chemotherapy; CI, confidence interval; EFS, event-free survival; ITT, intention to treat; NIVO, nivolumab; NR, not reached; PBO or Pla, placebo.

Source: BMS data on file (9)

4.3.1.2 Overall survival

Overall survival (OS) in CheckMate-77T was defined as the time between the date of randomisation and the date of death due to any cause and OS was censored on the last date a patient was known to be alive.[15]

At the 16 December 2024 database lock, median OS [redacted] and the difference between treatment arms [redacted] (Table 6, Figure 3). The EAG notes from the company response to clarification question A13, that the final analysis of OS is planned at approximately 174 events which is anticipated to be in [redacted].

Table 6. CheckMate-77T: overall survival—all randomly assigned patients (ITT population) (Reproduced from Table 11 of the CS)

Events, n (%)	[redacted]		[redacted]
Median OS (95% CI, months)	[redacted]		[redacted]
HR (97.63% CI)		[redacted]	
HR (95% CI)		[redacted]	
P value		[redacted]	
24 months, %	[redacted]		[redacted]
30 months, %	[redacted]		[redacted]

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intention to treat; n, number; NR, not reached.

* Based on the data source, the EAG assumes this p value is for the 97.63% CI

Source: BMS data on file (9)

Figure 3. CheckMate-77T: overall survival—all randomly assigned patients (ITT population) (Reproduced from Figure 9 of the CS)

Abbreviations: Chemo, chemotherapy; CI, confidence interval; EFS, event-free survival; ITT, intention to treat; NIVO, nivolumab; NR, not reached; PBO or Pla, placebo.

Source: BMS data on file (9)

4.3.1.3 Pathologic response

Pathologic complete response (pCR) by blinded independent pathology review (BIPR) was defined as the absence of residual viable tumour in lung and lymph nodes as evaluated by BIPR. The EAG notes that the data reported in the CS for this outcome are from an earlier database lock (6 September 2023) than those for EFS and OS (16 December 2024). The proportion of patients with a pCR per BIPR in the nivolumab group (25.3%) was higher than in the chemotherapy group (4.7%; Table 7).

Patients who achieved a major pathological response (MPR) had ≤ 10% residual viable tumour in lung and lymph nodes. Similar to pCR per BIPR, a higher proportion of patients in the nivolumab group (35.4%) had a MPR by BIPR compared to in the chemotherapy group (12.1%; Table 7).

Table 7. CheckMate-77T: pathological complete response (per BIPR) and major pathological response (per BIPR)–all randomly assigned patients (ITT population) (Reproduced from Table 12 of the CS)

Pathologic complete response[a] per BIPR			
Responders, n (%)	58 (25.3)		11 (4.7)
95% CI[b]	19.8 to 31.5		2.4 to 8.3
Difference (95% CI)[c,d]		20.5 (14.3 to 26.6)	
Estimate of odds ratio (95% CI)[d,e]		6.64 (3.40 to 12.97)	
Major pathologic response[a] per BIPR			
Responders, n (%)	81 (35.4)		28 (12.1)
95% CI[b]	29.2 to 41.9		8.2 to 17.0
Difference (95% CI), %[c,d]		23.2 (15.8 to 30.6)	
Estimate of odds ratio (95% CI)[d,e]		4.01 (2.48 to 6.49)	

Abbreviations: BIPR, blinded independent pathology review; CI, confidence interval; ITT, intention to treat; n, number

[a] Randomly assigned patients who were no longer eligible for surgery, or who were on alternative anticancer therapy before surgery, or who discontinued the study before surgery were all counted as non-responders. In both arms, < 5% of randomly assigned patients did not provide tumour samples after surgery.

[b] Confidence interval based on the Clopper and Pearson method.

[c] Strata-adjusted difference based on Cochran–Mantel–Haenszel method of weighting.

[d] Stratified by randomisation stratification factors (tumour PD-L1 status [≥ 1% vs. < 1%/not evaluable/ indeterminate], disease stage [II vs. III], histology [squamous vs. non-squamous] per IRT).

[e] Strata-adjusted odds ratio using Mantel–Haenszel method.

Sources: BMS data on file (15); Cascone, Awad (13)

4.3.1.4 Objective response rate

Objective response rate (ORR) was also reported at the 6 September 2023 database lock. The EAG notes that the BICR ORR and the investigator-assessed ORR [redacted] (Table 8).

Table 8. CheckMate-77T: objective response rate and best overall response: all randomly assigned patients (ITT population) (Adapted from Table 13 of the CS)

Objective response rate per BICR, n (%)[a] 95% CI	133 (58.1) (51.4 to 64.5)		99 (42.7) (36.2 to 49.3)
Objective response rate per investigator-assessed, n (%)[a] 95% CI	[redacted]		[redacted]
Odds ratio for BICR (95% CI)		1.90 (1.30-2.76)	

Odds ratio for investigator-assessed (95% CI)	[redacted]	
Best overall response per BICR, n (%)		
Complete response	7 (3.1)	6 (2.6)
Partial response	126 (55.0)	93 (40.1)
Stable disease	73 (31.9)	107 (46.1)
Progressive disease	9 (3.9)	13 (5.6)
Unable to be determined	14 (6.1)	13 (5.6)

Abbreviations: BICR, blinded independent central review; CI, confidence interval; ITT, intention to treat; n, number

Confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing.

[a] Objective response was defined as complete response or partial response according to Response Evaluation Criteria in Solid Tumours, version 1.1, before definitive surgery without confirmation.

4.3.1.5 Event-free survival on next line of therapy per investigator

At the 6 September 2023 database lock, median event-free survival on next line of therapy (EFS2) per investigator had not been reached in either trial arm (CS table 15 and Figure 12) and results for EFS2 were not reported from the latest data-cut. The HR for EFS2 per investigator favoured the nivolumab group over the chemotherapy group, although it was not statistically significant (HR 0.83, 95% CI: 0.56 to 1.23), and are based on immature data. The EAG therefore recommends these results are interpreted with caution.

4.3.1.6 Health-related quality of life

The results for health-related quality of life (HRQoL) reported in the CS were limited to EQ-5D-3L VAS score and were reported using the 6 September 2023 database lock.

The company reported that after controlling for baseline score and relevant covariates, patients in the nivolumab and chemotherapy arms had small improvements (increase) in EQ-5D-3L VAS scores overall (during the neoadjuvant, surgical, and adjuvant periods). The change from baseline least squares mean was 1.07 (95% CI: −0.46 to 2.61) for the nivolumab group versus 1.67 (95% CI: 0.14 to 3.19) for the chemotherapy group. The EAG notes that the difference in mean change in EQ-5D-3L VAS scores from baseline for nivolumab versus chemotherapy was [redacted]

The EQ-5D-3L Utility Index Score results were reported in the clinical study report and for the overall trial period the difference in mean change from baseline for the nivolumab group compared to the chemotherapy group was [redacted]

4.3.2 NADIM-II

The median follow-up in NADIM-II was 26.1 months which is [redacted] than the median follow-up in the [redacted] data-cut from CheckMate-77T (median follow-up of [redacted]) available for EFS and OS outcomes.

4.3.2.1 Pathological complete response

Pathological complete response (pCR) was the primary endpoint in NADIM-II and was determined by BICR. In the intention-to-treat (ITT) population, 37% of patients in the nivolumab group had a pCR compared with 7% of patients in the chemotherapy group. Perioperative nivolumab resulted in a significantly higher percentage of patients with a pCR compared to chemotherapy alone (relative risk 5.34, 95% CI: 1.34 to 21.23; p=0.02).

4.3.2.2 Progression-free survival

Progression-free survival (PFS) was defined as the time from randomisation to progression of disease, recurrence of disease, or death from any cause and the EAG notes that PFS was not reported in CheckMate-77T.

At 24 months, PFS was 67.2% (95% CI, 55.8%-81.0%) in the nivolumab group and 40.9% (95% CI, 26.2%-63.6%) in the chemotherapy group of NADIM-II. Median PFS was not reached in the nivolumab group and was 15.4 months in the chemotherapy-alone group. The HR for PFS in NADIM-II suggests a statistically significant longer PFS with perioperative nivolumab compared to chemotherapy (HR 0.47; 95% CI: 0.25 to 0.88).

4.3.2.3 Overall survival

At the time of analysis, median OS had not been reached in either group of NADIM-II, but the HR favoured perioperative nivolumab compared to chemotherapy (HR 0.43; 95% CI: 0.19 to 0.98).

4.3.3 Subgroup analyses

Subgroup analyses for EFS by BIRC were reported for disease stage, PD-L1 status and tumour histology (Table 9).

[redacted]

[redacted] over the comparative effectiveness of nivolumab and placebo for these groups.

In response to clarification questions (CQs), the company provided subgroup analysis for investigator-assessed EFS (Company response to CQs Appendix 4). Results for disease stage and PD-L1 status [redacted]

Table 9. Subgroup analysis of the CheckMate-77T trial – EFS by BICR (ITT population) (Reproduced from Table 7.2.2.1-1 of CheckMate-77T CSR)

Subgroups	HR (95% CI)[a,b]
Disease stage at entry	
II	[redacted]
III	[redacted]
PD-L1 status	
<1%	[redacted]
≥1%	[redacted]
Tumour histology	
Squamous	[redacted]
Non-squamous	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; PD-L1, Programmed Death-Ligand 1

The company also provided OS results by trial stratification factor subgroups but due to the immaturity of the data, the company reported that the results should be interpreted with caution. The EAG notes that the results [redacted] (Table 10).

Table 10. CheckMate-77T subgroup results for OS by trial stratification factors (Reproduced from company response to clarification question A16)

4.4 Critique of the indirect treatment comparison

4.4.1 Critique of trials identified and included in the indirect treatment comparison

The company's SLR searched for RCT evidence for nivolumab or other types of immunotherapy, targeted therapy or chemotherapy, with or without radiotherapy for the treatment of people with resectable non-metastatic (stages I-III) NSCLC. The EAG notes that the ITCs reported in the CS were conducted using a restricted network of trials from a wider network, that included additional studies reporting on treatments outside the NICE final scope. As discussed in Section 4.1, three studies that reported on interventions relevant to the decision problem were included in the ITCs reported in the CS, two of which assessed the effects of perioperative nivolumab (CheckMate-77T and NADIM-II), while one assessed perioperative pembrolizumab (KEYNOTE-671).

As discussed in Section 4.2 for the nivolumab trials, the EAG agrees with the company's assessment of the risk of bias for CheckMate-77T, but has concerns about NADIM-II, particularly regarding the population and dosing regimen, which may limit its relevance to NHS clinical practice. Assessment of

the quality of the evidence for the pembrolizumab trial (KEYNOTE-671) is presented in Table 11. While there are limited concerns about the methods used for KEYNOTE-671, it should be noted that, unlike CheckMate-77T, patients were not excluded if they had confirmed anaplastic lymphoma kinase (ALK) translocations. The EAG's clinical experts highlighted how patients who have ALK translocations are typically offered targeted therapies rather than immunotherapy in clinical practice, due to limited evidence on the benefits of immunotherapy in these patients. However, as only a small percentage of patients in KEYNOTE-671 had confirmed ALK translocations (3% in the pembrolizumab arm and 2% in the placebo arm) this appears unlikely to have had a major impact on the results of the ITCs.

Table 11. EAG's summary of the design, conduct and analysis of KEYNOTE-671

Aspect of trial design or conduct	Location in which information is reported	EAG's critique
Randomisation	Spicer *et al.* 2024	**Appropriate** Patients were randomised using 1:1 randomisation using an interactive response system. Patients were stratified by disease stage (II, III), PD-L1 tumour proportion score (<50%, ≥50%), tumour histology (squamous, non-squamous) and geographical region (east Asia, other).
Concealment of treatment allocation	Spicer *et al.* 2024	**Appropriate** The study was double-blind, with access to treatment allocation only available to an unblinded pharmacist involved in treatment preparation but otherwise not involved in the care of study patients.
Eligibility criteria	Spicer *et al.* 2024, Supplementary Appendix, Section 6.1	**Appropriate** Inclusion criteria: • Males and females aged ≥ 18 years • Previously untreated and pathologically confirmed resectable stage II, IIIA or IIIB (N2) NSCLC (according to AJCC 8th edition) • Able to undergo protocol therapy, including necessary surgery
Baseline characteristics	Spicer *et al.* 2024	**Appropriate** Most baseline characteristics were balanced across arms, with marginal differences for the percentage of patients with clinical node stage N2 (42% for pembrolizumab, 47% for placebo) and ALK translocation (No known ALK translocation: 26% for pembrolizumab, 33% for placebo; Unknown: 71% for pembrolizumab, 65% for placebo).
Dropouts	Spicer *et al.* 2024	**Some concerns** A relatively high percentage of patients did not receive all four administrations of either pembrolizumab or placebo, but this was balanced across trial arms (26% in each arm).

Aspect of trial design or conduct	Location in which information is reported	EAG's critique
Statistical analysis		
Sample size and power	Spicer *et al.* 2024	**Appropriate** The study was designed to have 90.1% power to detect a HR of 0.70 with a one-sided type I error of 0.01, according to the observation of 416 patients with event-free survival events and two analyses. The planned sample size was 786 and a total of 797 patients were randomised to study treatments.
Handling of missing data	Spicer *et al.* 2024, Supplementary Appendix, Section 3.6.3.4	**Appropriate** Between-group differences for change from baseline outcomes were estimated using a missing at random analysis. Where data were missing for between-group differences in the percentage of patients with improved or stable GHS/quality of life, missing data were considered to reflect no improvement or stability.
Outcome assessment	Spicer *et al.* 2024 Spicer *et al.* 2024, Supplementary Appendix, Protocol amendment 10	**Some concerns** Clinical response outcomes were assessed using measures that are commonly used in practice or research. However, while the primary outcome was EFS, this was modified during the trial from BICR to evaluation by a local pathologist or investigator-assessed imaging. The EAG notes that the company identified separate results for investigator-assessed and BICR-assessed EFS, but these were for different time points in the trial. This is discussed in more detail in Section 4.5.1.

Abbreviations: ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; EAG, external assessment group; EFS, event-free survival; HR, GHS, global health status; hazard ratio; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1

The EAG's clinical experts considered the choice of subsequent treatments in both trials to be broadly reflective of NHS clinical practice (Table 12). The EAG notes that limited data was reported in KEYNOTE-617 about the proportion of subsequent treatments received in the ITT population, which restricts the comparisons that can be made between the two trials. Comparisons could not be made with NADIM-II which did not report the proportion of the ITT population who received subsequent therapies. Based on the percentage of patients who received ≥1 subsequent therapy, and the percentage who received anti-PD1 or anti-PDL1 therapies, the EAG's clinical experts considered CheckMate-77T to be most reflective of NHS clinical practice.

Table 12. Subsequent therapies reported in the CheckMate-77T and KEYNOTE-617 trials

	Nivolumab	Placebo	Pembrolizumab	Placebo
≥1 subsequent therapy	23.1%	37.5%	30%	52%
Surgery	2.6%	3.0%	NR	NR

Radiotherapy	12.2%	19.4%	NR	NR
Systemic therapy	17.5%	31.5%	NR	NR
Platinum-based chemotherapy	10.0%*	19.8%*	NR	NR
Anti-PD1 or anti-PDL1	7.0%†	22.8%†	8%	29%

* carboplatin, cisplatin or nedaplatin

† atezolizumab, camrelizumab, dostarlimab, durvalumab, nivolumab, pembrolizumab, sintilimab, tislelizumab, topipalmab or TQ B2450

Abbreviations: NR, not reported; PD-L1, programmed death-ligand 1

Based on the NICE final scope and the advice of clinical experts, the EAG notes that both perioperative pembrolizumab and perioperative durvalumab could be considered comparators for perioperative nivolumab. The EAG also notes that the key trial used to inform the NICE TA1030 guidance for durvalumab is the AEGEAN trial and this trial was identified by the company's SLR.

In the clarification questions, the EAG requested updated ITCs including only the three trials which were most relevant to the decision problem (CheckMate-77T, KEYNOTE-671 and AEGEAN). The NADIM-II study was excluded from the updated ITCs due to concerns about its relevance to NHS clinical practice (as discussed in Section 3). A comparison of the studies included in the updated ITCs, including trial design, treatments and doses, are presented in Table 13. As the company considered pembrolizumab to be the key comparator for the analysis, the EAG's critique in the following sections focuses on the results from CheckMate-77T and KEYNOTE-671. The EAG provided an addendum to the EAG report where the ITC results including durvalumab are discussed.

Table 13. Overview of studies included in the company's updated ITCs.

CheckMate-77T	461	3.4	Neoadjuvant treatment: • Nivolumab 360 mg every 3 weeks + standard of care chemotherapyfor up to 4 cycles Adjuvant treatment: • Nivolumab 480 mg every 4 weeks for up to 13 cycles (approximately 1 year)	Neoadjuvant treatment: • Placebo every 3 weeks + standard of care chemotherapyfor up to 4 cycles as neoadjuvant therapy followed by surgery Adjuvant treatment: • Placebo every 4 weeks for up to 13 cycles (approximately 1 year) after surgery
KEYNOTE-671	797	3.4	Neoadjuvant treatment: • Pembrolizumab 200 mg every 3 weeks for four	Neoadjuvant treatment: • Placebo every 3 weeks for four cycles in combination

			cycles in combination with cisplatin 75 mg/m² every 3 weeks and either gemcitabine 1000 mg/m² on days 1 and 8 Adjuvant treatment: • Pembrolizumab 200 mg every 3 weeks for up to 13 cycles	with cisplatin 75 mg/m² every 3 weeks and either gemcitabine 1000 mg/m² on days 1 and 8 Adjuvant treatment: • Placebo every 3 weeks for up to 13 cycles
AEGEAN	740	2.2	Neoadjuvant treatment: • Durvalumab 1500 mg every 3 weeks for four cycles in combination with platinum-based chemotherapy Adjuvant treatment: • Durvalumab 1500 mg every 4 weeks for up to 12 cycles	Neoadjuvant treatment: • Placebo every 3 weeks for four cycles in combination with platinum-based chemotherapy Adjuvant treatment: • Placebo every 4 weeks for up to 12 cycles

Abbreviations: m, metres; mg, milligrams

4.4.2 Critique of the methods used for the indirect treatment comparison

The company conducted ITCs to compare perioperative nivolumab with perioperative pembrolizumab and reported that the ITCs were performed as part of a global project assessing treatment efficacy across multiple treatments of patients with stage II-IIIB resectable non-metastatic NSCLC. The company reported results from three different methods of analysis in the CS:

1) a traditional Bayesian network meta-analysis (NMA);
2) a fractional polynomial (FP)–NMA, which relaxed the proportional hazards (PH) assumption required by traditional Bayesian NMA; and
3) a multilevel network meta-regression (ML-NMR) to generate estimates of relative effect adjusted to the population in CheckMate-77T.

The company has conducted the ITCs using two datasets for perioperative nivolumab versus perioperative pembrolizumab – one including CheckMate-77T, NADIM-II and KEYNOTE-671, and the other excluding NADIM-II.

The primary outcomes of interest in the company's ITCs were EFS and OS. The EAG notes that all the analyses reported by the company were conducted using the statistical software R[16]. For the NMA, the files provided by the company allowed analyses to be run, but the EAG does not consider the

code provided to be sufficient to produce the required outputs for the EAG to fully validate the company's results or model fit. The EAG has therefore conducted independent validation of the company's Bayesian NMA using the Bucher ITC method for the analyses of EFS and OS using only data from CheckMate-77T and KEYNOTE-671 (i.e. excluding NADIM-II). However, the EAG was unable to conduct its own FP-NMAs or validate the company's FP-NMA analyses due to time constraints and the volume of information (e.g. [redacted] from the company's code). The EAG also considers there to be a lack of detail provided to explain the FP-NMA code and the output files produced by it. In addition, the EAG did not have access to the individual patient-level data (IPD) required to undertake the validation of the ML-NMR.

The CS was accompanied by an NMA report that provided additional details on the company's ITCs. In the NMA report, it was explained that the proportional hazards assumption within each trial was evaluated through a visual inspection of the Kaplan-Meier (KM) data, log cumulative hazard plots, Schoenfeld residuals, and Grambsch-Therneau tests. The EAG notes that the company concluded that the assumption of PH [redacted]. In addition, the company reported [redacted]. In the CS, the company reported that the PH assumption was not rejected in CheckMate-77T and visual inspections did not suggest obvious deviations. The EAG considers that the violation of PH for NADIM-II adds further concern to the reliability of the results of the company's ITCs where NADIM-II has been included. The EAG therefore, reinforces its view that the results from the ITCs excluding NADIM-II are more reliable.

The EAG does not consider there to be sufficient evidence from the assessments of PH presented by the company to reject the assumption of PH for either CheckMate-77T or KEYNOTE-671. However, the EAG also acknowledges the company's concerns for KEYNOTE-671 and considers visual inspection of some of the log cumulative hazard plots to be inconclusive in terms of concluding PH, particularly for OS.

The EAG notes that the company reported results for the ITCs from fixed effects models, which the EAG considers to be reasonable given the sparsity of data in the network.

The EAG has further concerns around the data included from NADIM-II in the analyses of EFS as NADIM-II did not report EFS and so the company included data on PFS as a surrogate for EFS in each of the three original company ITCs (traditional Bayesian NMA, FP-NMA and ML-NMR). The company highlighted in the NMA report that the analyses of EFS from CheckMate-77T and KEYNOTE-671 used consistent definitions of EFS but used different methods of outcome assessment (BICR and investigator, respectively). In addition, the EAG notes that data from KEYNOTE-671 for EFS-BICR was only available using earlier data-cuts compared to the data used for EFS-INV in the company's original ITCs presented in the CS and the KEYNOTE-671 EFS-BICR data [redacted] compared with the data from CheckMate-77T. In contrast, the KEYNOTE-671 data used for EFS-INV from the later data-cut have [redacted] compared with the data used from CheckMate-77T for EFS-INV. The EAG notes that the results from CheckMate-77T [redacted] but nevertheless considers the use of a consistent dataset in terms of EFS assessment method to be more appropriate. The EAG also considers the use of the most mature data to be preferred in addition to the use of a consistent data-set. The EAG thus recommends caution in drawing conclusions from the company's ITCs of EFS. The EAG has conducted exploratory Bucher ITCs using data from CheckMate-77T and KEYNOTE-671 with consistent methods of assessment of EFS (Section 4.5.1).

Table 14. EFS Outcome definitions across studies (target population: PD-L1 all-comers stage II-IIIB) (Reproduced from table 8 of the NMA report)

[redacted]

4.4.3 Traditional Bayesian network meta-analysis

In the traditional Bayesian NMA, the HR for EFS [redacted] when NADIM-II was removed from the network [redacted] The EAG notes that the EFS results for nivolumab vs pembrolizumab [redacted]

[redacted]

The EAG considers the results from the company ITC including NADIM-II should be interpreted with caution given the violation of PH detailed in Section 4.2 as the NMA assumes a constant HR over time. In addition, while the EAG does not consider there to be sufficient evidence from the assessments of PH presented by the company to reject the assumption of PH for either CheckMate-77T or KEYNOTE-671, the EAG recommends caution in terms of drawing strong conclusions from the NMAs, particularly for OS.

Table 15. Traditional Bayesian NMA results for EFS and OS from the company's analyses

Intervention (vs. perioperative nivolumab)	Company original ITC including NADIM-II Fixed effect model HR (95% CrI)	Network excluding NADIM-II Fixed effect model HR (95% CrI)
Results for EFS		
periPEMBRO+neoCT	[redacted]	[redacted]
neoCT	[redacted]	[redacted]
Results for OS		
periPEMBRO+neoCT	[redacted]	[redacted]
neoCT	[redacted]	[redacted]

Abbreviations: CrI, credible interval; EFS, event-free survival; HR, hazard ratio; neoCT, Neoadjuvant chemotherapy; NMA, network meta-analysis; periNIVO+neoCT, Peri-operative nivolumab-neoadjuvant chemotherapy; periPEMBRO+neoCT, Peri-operative pembrolizumab-neoadjuvant chemotherapy.

4.4.4 Fractional polynomial network meta-analysis

The company conducted an FP-NMA to allow for non-linear modelling of treatment effects over time (time-varying HRs) for the outcomes of EFS and OS. The EAG notes that the FP-NMA is not dependent on a PH assumption holding and given the EAG's concerns regarding PHs the EAG considers the FP-NMA results may be more robust than the traditional Bayesian NMA results. However, as noted in Section 4.4.2, the EAG was unable to validate the results from the company's FP-NMAs.

4.4.4.1 FP-NMA EFS results

In the FP-NMA including NADIM-II, the company reported that the best-ranked model for EFS in terms of deviance information criterion (DIC) was a time-constant HR Weibull model. However, the company reported that after applying their predefined heuristic process that included 3 further assessments (reasonable model complexity, good alignment with the modelled versus observed survival curves based on visual inspection, and clinically plausible projections beyond the observed period), the final selected model was a second-order Weibull-based FP with powers of [redacted] and [redacted], and where treatment effects were placed on the [redacted]. The company reported that this was the best-ranked time-varying HR model based on DIC and the second-best model overall based on DIC. For the FP-NMA excluding NADIM-II (and including AEGEAN), the company concluded that the best-fitting non-PH model was a first-order Weibull-based fractional polynomial with powers [redacted], where treatment effects were applied to the first and third terms. However, the EAG considers the model to be a second-order FP model rather than first-order given it has two powers defined.

The EAG notes that the HRs of perioperative nivolumab relative to perioperative pembrolizumab [redacted] (Table 16). The FP-NMA results for the comparison between perioperative nivolumab and perioperative pembrolizumab in the company's original ITC including NADIM-II had a HR that [redacted] In the FP-NMA excluding NADIM-II [redacted] The EAG notes that the EFS results [redacted] Table 16[redacted]

Table 16. Event-free survival hazard ratios of perioperative nivolumab versus perioperative pembrolizumab over time in the fractional polynomial network meta-analysis (Adapted from table 17 of the CS and table 18 of the company response to clarification questions)

Time	Company original ITC including NADIM-II HR (95% CrI)	Network excluding NADIM-II HR (95% CrI)
3	[redacted]	[redacted]

6	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]
36	[redacted]	[redacted]
42	[redacted]	[redacted]
48	[redacted]	[redacted]
54	[redacted]	[redacted]
60	[redacted]	[redacted]

[redacted]

4.4.4.2 FP-NMA OS results

For the company's FP-NMA for OS including NADIM-II, the final selected model was a second-order Weibull-based FP with powers of [redacted] and [redacted], and treatment effects were placed on the first and third terms. For the FP-NMA excluding NADIM-II (and including AEGEAN), the company reported that the best-fitting non-PH model was a first-order fractional polynomial with powers [redacted], where treatment effects were applied to the first and second terms. However, the EAG considers the model is a second-order FP model rather than first-order given it has two powers defined.

The EAG notes that the HRs of perioperative nivolumab relative to perioperative pembrolizumab from the FP-NMAs [redacted] months (Table 17). The EAG notes that median follow-up in CheckMate-77T and KEYNOTE-671 for data used in this analysis was [redacted] and the company highlighted that the HRs at later time points should thus be interpreted with caution due to high censoring and limited follow-up.

With respect to the comparison between perioperative nivolumab and perioperative pembrolizumab, in the FP-NMA including NADIM-II the HRs [redacted] In the FP-NMA excluding NADIM-II [redacted]

Table 17. Overall survival hazard ratios of perioperative nivolumab versus perioperative pembrolizumab over time in the fractional polynomial network meta-analysis (Adapted from table 18 of the CS and table 19 of the company response to clarification questions)

Time	Company original ITC including NADIM-II Fixed effect model HR (95% CrI)	Network excluding NADIM-II Fixed effect model HR (95% CrI)
3	[redacted]	[redacted]
6	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]
36	[redacted]	[redacted]
42	[redacted]	[redacted]
48	[redacted]	[redacted]
54	[redacted]	[redacted]
60	[redacted]	[redacted]
[redacted]		

4.4.1 *Multilevel network meta-regression*

The company conducted an ML-NMR with limited adjustments for imbalances in patient populations across trials in the network. The company raised particular concerns in the CS that the proportion of patients with Stage III disease at baseline and the proportion of patients with PD-L1 expression levels ≥ 1% in KEYNOTE-671 was higher compared with CheckMate-77T. The company, therefore, considered an ML-NMR to be the most methodologically robust ITC approach for comparing perioperative nivolumab with perioperative pembrolizumab. The EAG also considers the ML-NMR to be a reasonable method to compare perioperative nivolumab with perioperative pembrolizumab given the potential concerns around [redacted] highlighted in Section 4.4.2.

The company reported that the characteristics for adjustment used in the ML-NMR were identified using clinical input, evidence collected from an SLR, and external evidence identified in advanced NSCLC populations. Disease stage was identified as a prognostic factor and PD-L1 expression level was identified as an effect modifier and therefore both were adjusted for in the company's ML-NMR using the population characteristics in CheckMate-77T. The EAG considers it to be unclear whether [redacted] was also included as an adjustment factor in the company's original ML-NMR

[redacted]

Table 18 summarises the baseline characteristics for Stage III and PD-L1 ≥ 1% in each of the three studies included in the company's original ML-NMR.

The EAG considers that adjusting for all potential prognostic and treatment effect modifiers (and so all available baseline characteristics) would have been a more robust approach, thus requested that the company conducted a fully adjusted ML-NMR analysis in their clarification questions. The results of the fully adjusted ML-NMR are discussed below alongside the results of the company's original ML-MNR.

The company reported that the fully adjusted analysis included covariate adjustment for all key baseline characteristics reported across trials with the exception of age. Prognostic factors were: disease stage, ECOG performance status, sex, region, smoking status, histology, and PD-L1 expression level; and treatment effect modifiers were: PD-L1 expression level, disease stage, and region. The company also reported that age was very similar across trials (median age ranged from 63 to 66 years in AEGEAN, KEYNOTE-671, CheckMate-77T, and NADIM-II) and was well-balanced across trial arms. The EAG thus considers the omission of adjustment for age in the company's ML-NMR to be unlikely to have a clinically meaningful impact on the overall results.

Table 18. Key baseline characteristics across the network of evidence informing the multilevel network meta-regression by study (reproduced from Table 19 of the CS)

CheckMate-77T	Perioperative nivolumab + neoadjuvant chemotherapy (229), neoadjuvant chemotherapy (232)	65	56[a]
NADIM-II	Perioperative nivolumab +neoadjuvant chemotherapy (57), neoadjuvant chemotherapy (29)	100	52
KEYNOTE-671	Perioperative pembrolizumab + neoadjuvant chemotherapy (397), neoadjuvant chemotherapy (400)	70	64

PD-L1 = programmed cell death-ligand 1.

[a] Patients with non-evaluable PD-L1 expression level were assumed to have PD-L1< 1%, rather than being excluded or using imputation.

4.4.1.1 ML-NMR EFS results

The company reported that nine parametric forms (exponential, accelerated failure time Weibull, proportional hazards Weibull, Gompertz, lognormal, loglogistic, gamma, generalized gamma and M-

spline) were considered. Furthermore, the company reported that model fit was assessed using a network of trials, which comprised a wider network than that included in the final ML-NMR in the company submission. The model fit in this wider network was assessed using the model fit statistics, visual inspection, and clinical plausibility with the 4-knot M-spline model considered to be the top-fitting M-spline model. The EAG notes that the 4-knot M-spline non-PH model that had best fit did not adequately converge despite implementation updates to address non-convergence and therefore the next best-fitting model was selected. This was the 4-knot PH M-spline model, despite concerns that it potentially overfit to the tails of the KM EFS data. The EAG is concerned that the 4-knot PH M-spline model does not appear to be a good visual fit for the CheckMate-77T K-M data given that IPD from this trial is used in the ML-NMR (i.e. the ML-NMR does not appear to predict the underlying data very well, which the EAG considers to be a potential symptom of model misspecification). The EAG is also unclear whether adjustments were made to the model specification for the analyses of EFS as detailed in the NMA report Section 12.1. In the event adjustments have been applied, the EAG considers there to be a lack of detail on the adjustments (e.g. which priors were adjusted, how were these priors selected for adjustment, what was the evidence base for the informed priors, what was the justification for the *post hoc* adjustment?). The EAG is therefore concerned about the reliability of the results from the company's ML-NMRs for EFS.

The ML-NMR results for EFS for the comparison between perioperative nivolumab and perioperative [redacted] The EAG notes that the removal of NADIM-II from the network [redacted] The EAG considers the preferred analysis set to be the network excluding NADIM-II with adjustment for all covariates [redacted] *Table 19 [redacted]

Table 19. Event-free survival hazard ratios of perioperative nivolumab versus perioperative pembrolizumab over time in the multilevel network meta-regression (adapted from Table 20 of the CS and Table 9 of the company response to clarification questions)

	Company original ITC including NADIM-II HR (95% CrI)	Network excluding NADIM-II HR (95% CrI)	Network excluding NADIM-II and with all covariates HR (95% CrI)
6	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]

30	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]
54	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]

[redacted]

4.4.1.2 ML-NMR OS results

For the ML-NMR analysis of OS, the company's preferred model was [redacted] model. The EAG notes that the same model was used for all three ML-NMR analyses of OS [redacted]. As noted earlier, the EAG did not have access to the necessary data to enable validation of the results from the company's ML-NMR.

[redacted]

The HRs from the ML-NMR for the comparison between perioperative nivolumab and perioperative pembrolizumab [redacted] Table 20). For the company's original analysis, [redacted] The EAG notes that the OS results from the EAG preferred ML-NMR analysis set excluding NADIM-II and with adjustment for all covariates [redacted] *Table 20 Table 20. Overall survival hazard ratios of perioperative nivolumab verses perioperative pembrolizumab over time in the multilevel network meta-regression (adapted from Table 21 of the CS and Table 12 of the company response to clarification questions)

Time	Company original ITC including NADIM-II HR (95% CrI)	Network excluding NADIM-II HR (95% CrI)	Network excluding NADIM-II and with all covariates HR (95% CrI)
6	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]

30	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]
54	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]
[redacted]			

4.5 Additional work on clinical effectiveness undertaken by the EAG

4.5.1 EAGs Bucher ITCs

To validate the company's traditional Bayesian NMA results for perioperative nivolumab versus perioperative pembrolizumab, the EAG performed Bucher ITCs for OS and EFS, using EFS-BICR from CheckMate-77T and EFS-INV from KEYNOTE-671 [company dataset]. The EAG also conducted three additional Bucher ITCs using a consistent EFS-assessment method for EFS-INV, and EFS-BICR as follows:

- Using investigator-assessed EFS data from Checkmate-77T and KEYNOTE-671 (EFS-INV);
- Using BICR EFS data from Checkmate-77T and KEYNOTE-671 (using data from IA1 in KEYNOTE-671 [EFS-BICR 1]);
- Using BICR EFS data from Checkmate-77T and KEYNOTE-671 (IA2 in KEYNOTE-671 [EFS-BICR 2).

The EAG considers is important to highlight that the EFS-BICR data from KEYNOTE-671 originate from earlier data-cuts than the data from EFS-INV as detailed in Table 21. Results of the EAG's Bucher ITCs are reported in Table 21.

Table 21. Results of Bucher ITCs performed by the EAG comparing perioperative nivolumab with perioperative pembrolizumab

Outcome analysed in the Bucher ITC	Trial-level results HR (95% CI)		Bucher ITC HR (95% CI)
	Checkmate-77T: Nivolumab vs placebo	KEYNOTE-671: Pembrolizumab vs placebo	Nivolumab vs pembrolizumab
EFS (company dataset)*	[redacted]	0.57 (0.47 to 0.69)†	[redacted]
EFS (investigator-assessed)**	[redacted]	0.57 (0.47 to 0.69)†	[redacted]
EFS (BICR-assessed 1)‡	[redacted]	0.66 (0.53 to 0.83)§	[redacted]

EFS (BICR-assessed 2)[‖]	[redacted]	0.62 (0.51 to 0.76)[¶]	[redacted]
OS	[redacted]	0.73 (0.58 to 0.92)[†]	[redacted]

* BICR-assessed for CheckMate-77T and investigator-assessed for KEYNOTE-671 (KEYNOTE-671 data from 19 August 2024 database lock).

[**] Data for KEYNOTE-671 from 19 August 2024 database lock.

[†] Median follow-up of [redacted]

[‡] Data for KEYNOTE-671 from IA1 29 July 2022[20]

[§] median follow-up 25.2 months

[‖] Data for KEYNOTE-671 from IA2 10 July 2023[21]

[¶] Median follow-up 29.8 months

Abbreviations: BICR, blinded independent central review; CI, confidence interval; EFS, event-free survival; HR, hazard ratio, IA, interim analysis; ITC, indirect treatment comparison; OS, overall survival.

The Bucher ITCs conducted by the EAG generated similar results to the equivalent analyses conducted by the company (i.e. the company NMAs excluding NADIM-II). The EAG's results for EFS-INV [redacted].

The EAG recommends caution in interpreting the results from the analyses using EFS-BICR from KEYNOTE-671 [redacted] The EAG notes that the median follow-up for the EFS-INV data from CheckMate-77T and KEYNOTE-671 [redacted] As discussed in Section 4.4.2, the EAG considers the use of a consistent method of EFS-assessment along with the latest data cut to be preferred. However, based on the available data, the EAG prefers the use of EFS-INV as it has a later data cut than EFS-BICR, despite EFS-BICR typically being considered more reliable given the blinding of outcome assessment.

4.5.2 EAGs point-and-density plots

The EAG has conducted Bayesian NMAs using R (v4.2.0) to generate point-and-density plots for the comparison of perioperative nivolumab versus perioperative pembrolizumab. Point-and-density

plots provide additional evidence, beyond that presented in traditional forest plots, to aid assessments of non-inferiority where 95% credible intervals for the hazard ratio comparing two treatments overlap a non-inferiority margin (NIM) or minimal clinically important difference (MCID) threshold. Non-inferiority analyses are dependent on having a clinically validated threshold (i.e., NIM) that represents the maximum reduction in clinical effectiveness that is considered acceptable while still considering the treatments to be equal.[22] In the absence of a clinically validated threshold, it has been suggested that the threshold is set to either 0 for log hazard ratios or 1 for hazard ratios, which represents a more conservative estimate compared to if a clinically validated threshold is available.

To generate point-and-density plots, the following process was followed. Firstly, density plots were created, and these were then used to generate an empirical cumulative density function (ECDF). The ECDF is then used to determine the cumulative density of any point between the minimum and maximum log hazard ratio for the comparison of perioperative nivolumab to perioperative pembrolizumab. The ECDF can be used to determine the number of iterations from the Bayesian analysis that fall below a given threshold (e.g., NIM or MCID) and thus the probability that the hazard ratio falls below the given threshold. When interpreting such probabilities, it has been suggested that a probability of 95% is used to make assessments of non-inferiority.[23]

The point-and-density plots then combine the results of the ECDF with those of a traditional density plot and forest plot. On the point-and-density plot, the point and error bars represent the corresponding log hazard ratio, and 95% credible intervals, as estimated from the NMA. The EAG has used fixed effects (FE) models for all analyses due to the small number of trials in the NMAs (CheckMate-77T and KEYNOTE-671). The EAG NMAs were run using 5 chains with a burn-in period of 10,000 iterations followed by 100,000 iterations per chain. The company did not report a NIM or MCID for either EFS or OS and therefore the EAG has used a threshold of 0 on the log-axis (which corresponds to a hazard ratio of 1). As discussed above, the setting of the threshold to 0 represents a conservative threshold by which to assess non-inferiority, although this represents the most appropriate threshold in the absence of a clinically validated NIM or MCID. Additionally, the probabilities reported on the point-and-density plots correspond to the probability that nivolumab is non-inferior compared to a comparator, when using the threshold of 0 on the log-axis (i.e., a hazard ratio of 1). As such, in this specific scenario, the probability of non-inferiority can be interpreted as the probability that the hazard ratio is in favour of nivolumab, or in favour of pembrolizumab.

The EAG has produced point-and-density plots for the outcomes of EFS and OS. The EAG has limited the EFS analyses to those consistent with the company's preferred EFS analysis set (EFS-company dataset), and those for EFS-INV and EFS-BICR using the latest available data-cut (EFS-BICR 2). It should be noted that the analyses for the point-and-density plots uses Bayesian NMA methodology and thus assumes PH.

[redacted]

4.5.2.1 Point-and-density plot results for EFS

As shown by the point-and-density plot (Figure 4),

[redacted] The results for EFS-

[redacted] Figure 5). In terms of EFS-BICR, using the latest available data-cut for KEYNOTE-671 with data available for this outcome, the probability of non-inferiority is [redacted] Figure 6 [redacted] As discussed in Section 4.4.2, the EAG considers the use of a consistent method of EFS-assessment along with the latest data cut to be preferred. Based on the available data, the EAG prefers the use of EFS-INV as it has a later data cut than EFS-BICR, despite EFS-BICR typically being considered more reliable given the blinding of outcome assessment.

Figure 4. Point-and-density plot for the comparison of perioperative nivolumab to perioperative pembrolizumab for EFS using the company preferred dataset.

Figure 5. Point-and-density plot for the comparison of perioperative nivolumab to perioperative pembrolizumab for EFS-INV.

Figure 6. Point-and-density plot for the comparison of perioperative nivolumab to perioperative pembrolizumab for EFS-BICR 2.

[redacted]

4.5.2.2 Point-and-density plot results for OS

The point-and-density plot for OS (Figure 7)

[redacted]

Figure 7. Point-and-density plot for the comparison of perioperative nivolumab to perioperative pembrolizumab for OS.

[redacted]

4.6 Adverse effects

The CS highlighted that while the frequency of AEs in CheckMate-77T was similar between trial arms, the frequency of serious AEs and AEs leading to treatment discontinuation were [redacted] with nivolumab than placebo (Table 22). There were few Grade 5 AEs, with [redacted] for nivolumab ([redacted]) and [redacted] for placebo ([redacted]). Although a [redacted] percentage of patients died in the nivolumab arm as a result of NSCLC [redacted] compared to [redacted] with placebo), [redacted] patients died as a result of study drug toxicity with nivolumab ([redacted]) while [redacted] died from drug toxicity in the placebo arm.

Table 22. AEs reported in the CheckMate-77T trial (Reproduced from Table 23 of the CS)

	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
All AEs (all causality), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All AEs leading to discontinuation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All serious AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery related AE,[a] n = 178 in each arm, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; n, number

[redacted]

The Summary of Product Characteristics (SPC) for nivolumab reports that, when nivolumab is used in combination with chemotherapy, the most frequent AEs (occurring in 10% or more of patients) are nausea, fatigue, peripheral neuropathy, decreased appetite, constipation, diarrhoea, vomiting, rash, stomatitis, abdominal pain, musculoskeletal pain, pyrexia, cough, oedema and pruritis. This is widely reflected by the AEs reported by the company, although [redacted] were also commonly reported (occurring in 15% or more of patients) (Table 23). The EAG's clinical experts discussed how it would have been more useful to have seen

AEs differentiated by those considered to be immune-related and those likely to be chemotherapy-related. However, this information was not provided in the CS.

Table 23. Most common AEs reported in the CheckMate-77T trial (adapted from Table 8.1.1-1 in the CSR)

	Any grade	Grade 3-4	Any grade	Grade 3-4
All-cause AEs				
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Decreased neutrophil count	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; n, number

The most common treatment-related AEs (occurring in ≥15% of patients) with nivolumab were anaemia, nausea, alopecia, constipation, fatigue and decreased neutrophil count (Table 24). A similar percentage of patients in each arm experienced treatment-related AEs, few of which were classed as Grade 3-4. The greatest difference between trial arms was reported for decreased neutrophil count (Table 24), which was experienced by more patients in the nivolumab group than with placebo (a difference of [redacted] for any grade AE and [redacted] for Grade 3-4 AEs). The only treatment-related AE reported more commonly with placebo than nivolumab was nausea, which was experienced by [redacted] of placebo patients compared to [redacted] with nivolumab.

KEYNOTE-671 reported a wider range of common treatment-related AEs associated with pembrolizumab than were reported for nivolumab in CheckMate-77T. However, the percentage of patients experiencing an AE is not directly comparable, with KEYNOTE-671 reporting common AEs as those occurring in ≥10% of patients, compared to the ≥15% threshold reported for CheckMate-77T. Despite this, the difference between the percentage of treatment-related AEs reported for placebo and those reported for either nivolumab or pembrolizumab was similar (Table 24). The only treatment-related AE reported more commonly with nivolumab than pembrolizumab was alopecia

([redacted] with nivolumab, 9% with pembrolizumab). However, as discussed above, results were not separated by immunotherapy- or chemotherapy-related AEs. It is therefore difficult to establish if this difference was a result was due to a response to nivolumab, or whether it instead reflects the different chemotherapy regimens used in the trials. No common treatment-related AEs were reported for nivolumab that were not also reported for pembrolizumab.

Table 24. Most common treatment-related AEs reported in the CheckMate-77T and KEYNOTE-671 trials (adapted from Table 8.1.1-1 in the CSR)

	Nivolumab (n=228)	Placebo (n=230)	Pembrolizumab (n=396)	Placebo (n=399)
Any grade treatment-related AEs				
[redacted]	[redacted]	[redacted]	140 (35%)	134 (34%)
[redacted]	[redacted]	[redacted]	214 (54%)	203 (51%)
[redacted]	[redacted]	[redacted]	37 (9%)	41 (10%)
[redacted]	[redacted]	[redacted]	106 (27%)	100 (25%)
[redacted]	[redacted]	[redacted]	106 (27%)	93 (23%)
[redacted]	[redacted]	[redacted]	169 (43%)	167 (42%)
Grade 3-4 treatment-related AEs	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	29 (7%)	23 (6%)
[redacted]	[redacted]	[redacted]	7 (2%)	6 (2%)
[redacted]	[redacted]	[redacted]	0 (0%)	1 (<1%)
[redacted]	[redacted]	[redacted]	3 (1%)	0 (0%)
[redacted]	[redacted]	[redacted]	4 (1%)	3 (1%)
[redacted]	[redacted]	[redacted]	83 (21%)	79 (20%)

Abbreviations: AE, adverse event; n, number

* Treatment-related AEs occurring in ≥15% of patients

† Treatment-related AEs occurring in ≥10% of patients

4.7 Conclusions of the clinical effectiveness section

The company has submitted evidence in support of the clinical similarity of nivolumab to pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable NSCLC. The EAG notes that pembrolizumab has a similar mechanism of action to nivolumab and both drugs are administered using an intravenous (IV) infusion. The EAG considers perioperative pembrolizumab to be an appropriate comparator for consideration of the relative clinical efficacy and safety of perioperative nivolumab.

The company presented clinical evidence for perioperative nivolumab from the CheckMate-77T trial and the NADIM-II clinical trial, both of which compared the efficacy and safety of perioperative nivolumab to neoadjuvant chemotherapy. The EAG considers CheckMate-77T to be a high-quality RCT trial, which included the relevant population, intervention, comparators and outcomes to address the decision problem in the NICE final scope. The EAG's clinical experts considered that the population in CheckMate-77T is broadly consistent with that expected in clinical practice and that the interventions and comparators were relevant to practice in England. In contrast, the EAG considers there to be potential issues with the quality of NADIM-II, including that it was an open-label RCT and the EAG has issues with the generalisability of NADIM-II to clinical practice in England. The EAG has particular concerns surrounding the population and intervention in NADIM-II, due to the omission of Stage II patients from the trial and differences in the dosing regimen of perioperative nivolumab compared with the MHRA marketing authorisation.

The company presented evidence for outcomes of EFS, OS, response, health-related quality of life (HRQoL) and adverse effects. The EAG considers that CheckMate-77T provides evidence that EFS [redacted] with perioperative nivolumab compared to neoadjuvant chemotherapy. Data for OS are [redacted]

The EAG notes that frequency of AEs in CheckMate-77T was similar between trial arms [redacted] with nivolumab than placebo. A naïve comparison of the most common treatment-related adverse events (AEs) suggested AEs were similar between perioperative nivolumab and perioperative pembrolizumab. This view was also supported by the EAG's clinical experts.

No trials made direct head-to-head comparisons between perioperative nivolumab and perioperative pembrolizumab. The company therefore performed a series of ITCs that included traditional Bayesian NMAs, FP-NMAs and ML-NMRs. The EAG is concerned that the inclusion of NADIM-II in the company's ITCs leads to clinical heterogeneity within the networks and is also concerned with the generalisability of the results to the NHS. In addition, the EAG notes the company's conclusion that the [redacted]

[redacted]. The EAG, therefore, considers that the results from the ITCs excluding NADIM-II are more appropriate to assess the relative efficacy of nivolumab vs pembrolizumab in clinical practice in England. Consequently, the EAG requested that the company provided results from the ITCs excluding NADIM-II and including the AEGEAN study for durvalumab, which was listed as a comparator in the NICE final scope.

Overall, the EAG does not consider there to be sufficient evidence from the assessments of PH presented by the company [redacted]. However, the EAG also acknowledges the company's concerns for [redacted]. The EAG notes that the violation of the PH assumption for any outcomes would introduce a considerably level of uncertainty in the appropriateness of a traditional Bayesian NMA, which relies on PH.

The EAG also notes that for the analyses of EFS, the company has used data from CheckMate-77T for EFS-BICR and for EFS-INV from KEYNOTE-671 in all of the company's ITCs. The EAG considers that a consistent method of assessment for EFS across trials is preferred. Furthermore, data from KEYNOTE-671 for EFS-BICR [redacted] compared with the data from CheckMate-77T, [redacted] median follow-up. The EAG, therefore, considers that consistently using EFS-INV, as it is reported from a later data cut, in the ITCs is the preferred approach, although EFS-BICR could be considered more methodologically robust due to the blinding of the outcome assessment. NADIM-II did not report results for EFS. The EAG, therefore, recommends caution in drawing conclusions from the results of the ITCs for EFS where NADIM-II is included.

In terms of the FP-NMAs and the ML-NMRs, the EAG is unable to confirm the replicability of the results from either method of analysis due to time constraints for the FP-NMAs and because the company did not provide suitable files for the ML-NMR to enable validation.

For the ML-NMRs, the EAG is further concerned that the OS and EFS [redacted]

The results from the company's three ITCs excluding NADIM-II for EFS and OS [redacted] between perioperative nivolumab and perioperative pembrolizumab. [redacted] Given the EAG's concerns regarding PHs, the EAG considers the FP-NMA results is likely to be more robust than the traditional Bayesian NMA results. In addition, given the EAG's concerns about the reliability of the results from the company's ML-NMRs, the EAG considers the results from the FP-NMAs excluding NADIM-II are likely to be the most reliable source of efficacy estimates for perioperative nivolumab versus perioperative pembrolizumab. The EAG notes that in the FP-NMAs, excluding NADIM-II for EFS and OS [redacted]

The EAG conducted analyses to generate point-and-density plots for the EFS and OS results from standard NMA of data from CheckMate-77T and KEYNOTE-671. The company did not report a NIM or MCID for either EFS or OS and therefore the EAG has used a threshold of 0 (the equivalent of a HR of 1), which may represent a conservative threshold by which to assess non-inferiority. The findings from the EAG's analyses indicate [redacted] of non-inferiority for perioperative nivolumab compared to perioperative pembrolizumab for the outcomes of EFS using the company preferred dataset, EFS-INV and OS. It should be noted that the analyses for the point-and-density plots uses Bayesian NMA methodology and thus assumes PH. [redacted]

Overall, given the uncertainties in the ITCs, the EAG's view that the results from the FP-NMAs excluding NADIM-II are likely to be the most reliable results for perioperative nivolumab versus perioperative pembrolizumab for EFS and OS, and [redacted], the

EAG considers that the company has not provided robust evidence to demonstrate clinical similarity between nivolumab and pembrolizumab.

5 Summary of the EAG's critique of cost comparison evidence submitted

5.1 Cost assumptions

Underpinned by the assumption that nivolumab and pembrolizumab treated patient have similar health outcomes, the company has assumed that the following costs are also similar between treatments arms, leading to their exclusion from the company's cost comparison analysis;

- Adverse events;
- Health care resource use (hospitalisations, health care appointments and monitoring);
- Subsequent treatments;
- End of life costs.

Treatments acquisition and administration costs are the only costs which have been included in the company's analysis.

5.1.1 EAG critique

The EAG's clinical experts considered that nivolumab and pembrolizumab treated patients would be treated with similar subsequent treatments, require similar health care resources and have similar adverse event profiles and end-of-life costs. Therefore, the EAG considers their exclusion from the cost-comparison analysis to be appropriate.

When considering the uncertainty around the assumption of nivolumab and pembrolizumab treatment effects being similar, as discussed in detail in Section 4.7, if treatment effects are assumed to be dissimilar, the EAG considers that these costs should be included in the model, given they would lead to a difference in costs between treatments, due to the difference in treatment effects and discounting.

5.2 Interventions and comparators

In the company's base case, pembrolizumab was identified as the comparator of interest for the treatment of resectable non-small cell lung cancer, relative to nivolumab. However, as described in Section 4.7, the EAG's clinical experts considered durvalumab to also be a relevant comparator of interest. The EAG therefore provides an addendum to this report which considers durvalumab as a comparator to nivolumab as a scenario analysis.

5.3 Acquisition costs

The EAG has produced a confidential appendix to the EAG report which takes into account the confidential arrangements for pembrolizumab. The confidential appendix includes scenario analyses and the company and EAG base case results.

Treatment acquisition costs have been estimated in the company's analysis under the assumption that all patients will receive a full per-protocol course of neo-adjuvant and adjuvant treatments. The company's rational for this assumption was that as the nivolumab and pembrolizumab treatment effects are similar, they would result in equal durations of treatment.

Table 25 presents the estimated acquisition costs for each treatment arm across the neo-adjuvant and adjuvant settings. Dosing regimens for nivolumab were informed using CheckMate-77T,[13] with pembrolizumab dosing and treatment regimen being aligned to the KEYNOTE-671 trial and NICE TA1017.[3]

Table 25. Acquisition costs (adapted from Table 25 in the CS)

	Neoadjuvant	Adjuvant	Neoadjuvant	Adjuvant
Pharmaceutical formulation	10 mg/mL		100 mg	
Acquisition cost	£439 per vial		£2,630 per pack	
Method of administration	IV			
Doses	360 mg	480 mg	200 mg	200 mg (initial cycle) 400 mg (subsequent cycles)
Dosing frequency	Q3W	Q4W	Q3W	Q6W
Average length of a course of treatment	3 weeks	4 weeks	3 weeks	6 weeks
Average cost of a course of treatment	£3,951	£5,268	£5,260	£5,260 (initial cycle) £10,520 (subsequent cycles)
Number of repeat courses of treatment	4	13	4	7
Duration of treatment*	12 weeks	52 weeks	12 weeks	42 weeks
Total cost over treatment duration	£15,804	£68,484	£21,040	£68,380

Total cost of perioperative regimen	£84,288	£89,420

Abbreviations: IV, Intravenous; QxW, every x weeks.

*Includes length of course of final treatment after treatment administration

5.3.1 EAG critique

The EAG's clinical experts broadly agreed with the dosing regimens for nivolumab and pembrolizumab but noted that pembrolizumab patients would be followed up for closer to a year in the adjuvant setting. One of the EAG's experts stated that the pembrolizumab administration regimens may vary, with some patients being treated with eight cycles of 400mg Q6W, and others receiving three cycles of 200mg Q3W and then six cycles of 400mg Q6W. The company was therefore requested to conduct scenario analyses reflecting these regimes, with scenario results provided in Section 6.1.1. While the scenarios highlight the impact of the alternative dosing assumptions, the EAG considers that the pembrolizumab dosing regime in the company's base case is the most appropriate, given the alignment with NICE TA1017 and expected use in clinical practice.[3]

Given the lack of evidence provided in the CS to support the company's assumption that nivolumab and pembrolizumab patients would experience similar treatment discontinuation (with no patients discontinuing from treatment in the costing comparison analysis), the EAG requested the company to conduct a scenario which used the time to discontinuation (TTD) data from the company's ITC analysis. The company responded that the scenario could not be conducted as the company was unable to locate the TTD data for KEYNOTE-671.

While TTD from KEYNOTE-671 was unavailable, the company added that the similar nivolumab and pembrolizumab treatment effects supports the assumption of no difference in TTD between treatments, with the small difference in adverse event related discontinuation also supporting this assumption. The company noted that treatment related adverse event discontinuation was 12.6% for pembrolizumab patients in KEYNOTE-671, and 19.3% for nivolumab patients in CHECKMATE-77T.[13] The company suggested that while these figures may not directly represent TTD, they support discontinuation rates being similar between treatments, or perhaps slightly higher for nivolumab. Therefore, the company considered that not including TTD was a conservative assumption as nivolumab patients may be more likely to discontinue treatment due to adverse events, leading to lower treatment acquisition cost than reflected in the cost analysis. The EAG agrees with the

company that not including adverse event related discontinuation is therefore a conservative assumption, but only in the context of nivolumab and pembrolizumab treatment effects being similar. If instead treatment effects are dissimilar, then AEs will not be the only factor contributing to the difference in TTD, which would render excluding TTD no longer appropriate (and not necessarily a conservative assumption).

Overall, when assuming nivolumab and pembrolizumab treatment effects to be similar, the EAG notes that the acquisition costs for perioperative nivolumab are lower than the costs of perioperative pembrolizumab. In an adjuvant setting, nivolumab requires almost twice the number of course compared to pembrolizumab (13 compared to 7), where the average cost of a course of adjuvant nivolumab is approximately half that of pembrolizumab (£5,268 compared to £10,520), leading to similar costs in the adjuvant setting. However, because in the neo-adjuvant setting the same number of courses of treatment is given to nivolumab and pembrolizumab patients, and the cost of a course of nivolumab is lower than that of pembrolizumab, the nivolumab total acquisition costs are lower than those of pembrolizumab.

5.4 Administration costs

Administration costs were applied for each treatment administration as all treatments were provided intravenously. The company informed administration costs using NICE TA 1017,[3] which used cost codes SB13Z (Deliver more Complex Parenteral Chemotherapy at First Attendance) and SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance) from the National Cost Collection for the NHS (NCC),[24] to cost for administrations in the neo-adjuvant and adjuvant setting respectively. Table 26 presents the administration costs by treatment arm and setting.

Table 26. Administration costs (adapted from Table 26 in the CS)

	Nivolumab		Pembrolizumab	
	Neoadjuvant	Adjuvant	Neoadjuvant	Adjuvant
Source	National Cost Collection for the NHS (2024)[24]			
Cost sheet (service code)	Outpatient procedures (Medical oncology service and Clinical Oncology Service weighted costs)			
Cost code	SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance	SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance	SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance	SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance
Weighted costs	£190.69	£138.10	£190.69	£138.10
Number of units	4	13	4	7

Cost over the full-time horizon	£762.76	£1,795.34	£762.76	£966.72

Abbreviations: NHS, National Health Service

5.4.1 EAG critique

While the EAG agrees that the cost codes used are the same as those in NICE TA1017,[3] the EAG notes that TA1070 used the costs across all healthcare resources groups (HRG) in the NCC, opposed to only Outpatient Procedures, as in the company's base case. As according to the EAG's clinical experts, administrations can occur in the inpatient setting (day cases within admitted patient care) in addition to outpatient care, the EAG considers that the HRG costs may be the most appropriate source to inform administration costs, as was the approach in NICE TA1017.[3] The EAG requested the company to conduct a scenario using the costs from the HRG sheet in the NCC 2023/2024,[24] which was conducted as requested, leading to a decrease in the cost difference between treatments. Table 27 presents the administration costs across the difference costing approaches. In the EAG base case, the HRG administration costs have been assumed.

Table 27. Sources and values of administration costs

SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance	138	287	394
SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance	191	354	509
Source	NCC 2023/2024	NCC 2020/2021	NCC 2023/2024
Sheet	OPROC	HRG	HRG

Abbreviations: HRG, Healthcare Resource Group; OPROC, Outpatient procedures; NCC, National Cost Collection for the NHS.

The EAG additionally noted that cost code SB15Z (£430) from the NCC reflected the cost for subsequent elements of a chemotherapy cycle, while SB12Z and SB13Z are specific to the first appointment. The company was therefore requested to conduct a scenario using codes SB13Z and SB12Z to cost the initial administration for neo-adjuvant and adjuvant treatment respectively, followed by SB15Z for subsequent administrations. The company conducted the scenario, which led to a decrease in the difference in costs between treatments. The SB15Z cost from the HRG sheet in the NCC 2023/2024 is used to cost subsequent treatment administrations in the EAG base case.

6 Company and EAG cost comparison results

6.1 Company base case results

Table 28 presents the company base case results which show nivolumab to be cost saving relative to pembrolizumab.

Table 28. Company's base case results

Interventions	Acquisition costs (£)	Administration costs (£)	Total Costs (£)	Incremental costs (£)
Nivolumab	84,288.00	2,558.10	86,846.10	-
Pembrolizumab	89,420.00	1,729.48	91,149.48	−4,303.38

6.1.1 Company's scenario analyses

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions (discussed in Section 5 of the EAG report) to key model parameters including several analyses requested by the EAG at the clarification stage (Table 29).

Table 29. Outcomes of scenario analyses

Scenario	Nivolumab total costs (£)	Pembrolizumab total costs (£)	Incremental difference (£)
Company base case	86,846.10	91,149.48	−4,303.38
Adjuvant administration of pembrolizumab: eight cycles of 400mg Q6W	86,846.10	107,067.59	-20,221.49
Adjuvant administration of pembrolizumab: three cycles of 200mg Q3W and then six cycles of 400mg Q6W	86,846.10	101,945.69	-15,099.59
Use of HRG Administration costs	91,448.01	94,215.02	-2,767.01
Use of HRG Administration costs & Subsequent Elements of a Chemotherapy Cycle SB15Z	91,644.75	94,195.30	-2,550.55
Use of OPROC Administration costs & Subsequent Elements of a Chemotherapy Cycle SB15Z	87,964.90	91,757.66	-3,792.76

Abbreviations: HRG, Health Resource Group; OPROC, Outpatient Procedures; QxW, every x weeks.

6.2 EAG preference assumptions and base case results

Table 30 and Table 31 presents the EAG's preferred modelling assumptions and base case results. The EAG notes that these results are only applicable if a cost-comparison analysis between nivolumab and pembrolizumab is considers appropriate.

Table 30. EAG preferred modelling assumptions

Assumption	Nivolumab total costs (£)	Pembrolizumab total costs (£)	Independent incremental difference in costs (£)	Cumulative incremental difference in costs (£)
Company base case	86,846.10	91,149.48	−4,303.38	-
HRG administration costs	91,448.01	94,215.02	-2,767.01	-
Costing subsequent administration using cost code SB15Z	87,964.90	91,757.66	-3,792.76	-2,550.55

Abbreviations: EAG, External Assessment Group; HRG, Healthcare Resource Group

Table 31. EAG's base case results

Interventions	Acquisition costs (£)	Administration costs (£)	Total Costs (£)	Incremental costs (£)
Nivolumab	84,288.00	7,356.75	91,644.75	-
Pembrolizumab	89,420.00	4,775.30	94,195.30	-2,550.55

Abbreviations: EAG, External Assessment Group

6.3 Summary statement

Overall, the company and EAG base case results indicate that for the treatment of non-small cell resectable lung cancer, perioperative nivolumab is cost saving compared to perioperative pembrolizumab, with the cost saving driven by the difference in acquisition costs, specifically in the neoadjuvant setting. However, this is contingent on the assumption of clinical similarity between treatments being valid, which the EAG considers has not been demonstrated with sufficient robustness.

While nivolumab may be as effective and cost saving compared to pembrolizumab, additional feedback from the EAG's clinical experts stated that the differences in administrations in the adjuvant setting would be the greatest barrier to the uptake of nivolumab in clinical practice. Given the practical advantages, patients and clinicians are likely to continue to prefer to treat with pembrolizumab, as only seven treatment administrations are required, compared to the 13 treatment administrations for nivolumab.

7 Equalities and innovation

The company has not described any equalities or innovation considerations associated with nivolumab in the company submission.

8 EAG commentary of the robustness of the evidence submitted by the company

Clinical

The EAG considers that the company has not provided robust evidence of clinical similarity between perioperative nivolumab and perioperative pembrolizumab based on the results of the network meta-analyses (NMAs), fractional polynomial NMAs (FP-NMAs) and multilinear network meta-regression (ML-NMR) analyses. This conclusion is based on concerns regarding the results and reliability of the indirect treatment comparisons (ITCs) presented in the company submission (CS); the response to clarification questions; and the additional analyses conducted by the External Assessment Group (EAG). While the EAG notes the [redacted] The EAG notes that the company's clinical experts expected nivolumab and pembrolizumab to have similar treatment effects, but the EAG considers that ITCs are likely to provide a more robust method to compare the two treatments. [redacted]

The EAG considers particular areas of uncertainty or concern for the ITCs to include the following:

- The use of different EFS assessment methods from CheckMate-77T and KEYNOTE-671 in the company analysis of EFS;
- The inclusion of NADIM-II in the company's ITCs given its lack of generalisability to clinical practice in England;
- The use of NMA methods that assume proportional hazards (PH) given [redacted];
- The validity of the ML-NMR results due to the EAG's concerns [redacted]

[redacted];

- The EAG being unable to replicate the company's results including model selection for the FP-NMAs and the ML-NMRs due to time constraints and the lack of the necessary IPD data for the ML-NMR.

Given these uncertainties, and [redacted], the EAG considers that the company has not provided robust evidence to demonstrate clinical similarity between nivolumab and pembrolizumab.

The EAG notes that durvalumab is in the same position in the treatment pathway as pembrolizumab and so the EAG considers it to be a potentially suitable alternative comparator. Clinical efficacy data for durvalumab in this indication are available from the AEGEAN trial, and while it was included in ITCs reported in the company response to clarification questions, the company has not presented any formal comparison with durvalumab. The EAG presents its view on the clinical similarity of nivolumab to durvalumab in an addendum to this EAG report.

Economic

The EAG considers that the company's method for conducting the cost comparison analysis is appropriate, making the best use of the available data for nivolumab and pembrolizumab, from CheckMate-77T and KEYNOTE-671 respectively. However, the appropriateness of the approach is contingent on the assumption of clinical similarity between treatments being valid, which the EAG considers has not been demonstrated with sufficient robustness.

Nevertheless, if the nivolumab and pembrolizumab treatment effects are assumed to be similar, the company's and EAG's base case results identify nivolumab to be potentially cost saving.

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10 Appendices

10.1 Quality assessment of NADIM-II

Table 32. EAG's summary of the design, conduct and analysis of NADIM-II

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Provencio *et al*. 2023	**Unclear** Patients were randomised using 1:1 randomisation using a web-based registration and randomization system was used. No information is provided about stratification factors at randomisation.
Concealment of treatment allocation	CS – Section B.3.3.2, Table 7 Provencio *et al*. 2023	**Some concerns** The trial was open-label, meaning patients, clinicians and investigators were aware of treatment assignment. However, as all endpoints were objective outcomes and the primary endpoint (pathological complete response) was assessed by BICR it may not be a major concern.
Eligibility criteria	CS – Section B.3.3.2, Table 7	**Some concerns about disease stage** • Males and females aged ≥ 18 years • Histologically confirmed stage IIIA and potentially resectable locally advanced, stage IIIB (T3N2) NSCLC (AJCC 8th edition) • Tumour considered resectable before study entry • ECOG PS of 0-1 • Measurable or evaluable disease (according to RECIST 1.1 criteria) Patients in NADIM-II only included patients with stage III NSCLC who therefore had more severe disease than many patients in CheckMate-77T, which also included patients with resectable stage IIA to IIIB NSCLC.
Baseline characteristics	CS – Section B.3.3.2.1, Table 8	**Some concerns** There were a number of differences between trial arms. Some of these (sex, smoking status and histology) may not be a major concern. Others, such as node stage and tumour classification may be more of a concern. More patients in the nivolumab than placebo arm had a node stage of N2, which can result in worse outcomes than those with no nodal involvement. More patients had a tumour classification of T4 in the placebo than nivolumab group, indicating worse disease for patients in the placebo arm.
Dropouts	CS – Section B.3.3.2.1, Figure 7	**Appropriate** Dropouts were relatively low and similar across trial arms.
Statistical analysis		
Sample size and power	CS – Section B.3.2, Table 4	**Appropriate**

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
		The study was designed to have 80% power to detect a significant difference between groups at an alpha level of 0.05, according to a sample of 90 patients. A total of 90 patients were randomised to study treatments.
Handling of missing data	Provencio *et al*. 2023 - Statistical analysis plan	**Unclear** Missing data was treated as missing and was not imputed. No information is provided about the proportion of missing data.
Outcome assessment	CS – Section B.3.2 -Table 4	**Some concerns** Clinical response outcomes were assessed using measures that are commonly used in practice or research. However, NADIM-II reported PFS, which did not count patients who had surgery, even if they did not receive subsequent therapies. This does not fully align with the EFS outcomes reported in the CheckMate-77T and AEGEAN trials.

Abbreviations: AJCC, American Joint Committee on Cancer; BICR, blinded independent committee review; CS, company submission; EAG, External Assessment Group; ECOG, Eastern cooperative Oncology Group; EFS, event-free survival; ITC, indirect treatment comparison; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RECIST, response criteria in solid tumors

10.2 Baseline characteristics

10.2.1 CheckMate-77T

Table 33. CheckMate-77T: baseline characteristics of patients (Reproduced from Table 6 of the CS)

Age (years), median (range)	66.0 (37-83)	66.0 (35-86)
Male, n (%)	167 (72.9)	160 (69.0)
Race, n (%)[a]		
White	155 (67.7)	175 (75.4)
Black	4 (1.7)	4 (1.7)
Asian	66 (28.8)	50 (21.6)
Other	4 (1.7)	3 (1.3)
Geographic region, n (%)		
North America	23 (10.0)	21 (9.1)
Europe	123 (53.7)	127 (54.7)
Asia	65 (28.4)	50 (21.6)
Rest of the world [b]	18 (7.9)	34 (14.7)
ECOG PS [c]		

0	147 (64.2)	141 (60.8)
1	82 (35.8)	91 (39.2)
Disease stage, n (%) [d]		
IIA	15 (6.6)	18 (7.8)
IIB	66 (28.8)	63 (27.2)
IIIA	103 (45.0)	114 (49.1)
IIIB	43 (18.8)	35 (15.1)
Node stage, n (%)[e]		
N0	80 (34.9)	87 (37.5)
N1	56 (24.5)	52 (22.4)
N2	91 (39.7)	91 (39.2)
Single station	59 (25.8)	53 (22.8)
Multistation	31 (13.5)	38 (16.4)
Smoking status, %		
Never smoker	17 (7.4)	27 (11.6)
Current/former smoker	212 (92.6)	205 (88.4)
Histology, n (%)		
Squamous	116 (50.7)	118 (50.9)[f]
Non-squamous	113 (49.3)	114 (49.1)
Tumour PD-L1 expression		
< 1%	93 (40.6)	93 (40.1)
≥ 1%	128 (55.9)	128 (55.2)
1%-49%	83 (36.2)	76 (32.8)
≥ 50%	45 (19.7)	52 (22.4)
Not evaluable	8 (3.5)	11 (4.7)
Neoadjuvant platinum chemotherapy; n (%)[g]		
Cisplatin	55 (24.0)	42 (18.1)
Carboplatin	167 (72.9)	180 (77.6)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; n, number; PD-L1, programmed cell death-ligand 1

[a] Race was reported by the patients.

[b] This category includes Argentina, Australia, Brazil, and Mexico.

[c] ECOG PS scores range from 0-5, with higher scores indicating greater disability.

[d] Data for disease stage are from case-report forms, with staging criteria of the AJCC Staging Manual, 8th edition, used for classification.

[e] N3 node stage was reported in 2 patients (0.9%) in each treatment group.

[f] One patient (0.4%) in the chemotherapy group with a squamous tumour had a reported *EGFR* mutation; this finding was tested locally and could not be confirmed because of site closure interval.

[g] Five patients (2.2%) in the nivolumab group and 6 patients (2.6%) in the chemotherapy group switched from cisplatin to carboplatin. Neoadjuvant platinum chemotherapy was not reported in 2 patients (0.9%) in the nivolumab group and 4 patients (1.7%) in the chemotherapy group.

Sources: Cascone, Awad (13); BMS data on file (15)

10.2.2 NADIM-II

Table 34. NADIM-II: demographic and clinical characteristics of the patients at baseline (ITT population)[a] (Reproduced from Table 8 of the CS)

Age (years), median (IQR)	65 (58-70)	63 (57-66)
Male, n (%)	36 (63)	16 (55)
ECOG PS[a]		
0	31 (54)	16 (55)
1	26 (46)	13 (45)
Node stage, n (%)		
N0	6 (11)	9 (31)
N1	10 (18)	4 (14)
N2	41 (72)	16 (55)
N2, multiple stations	22 (39)	11 (38)
Smoking status, %		
Never smoker	5 (9)	0
Former smoker	22 (39)	8 (28)
Current smoker	30 (53)	21 (72)
Histology, n (%)		
Adenocarcinoma	25 (44)	11 (38)
Adenosquamous carcinoma	1 (2)	0
Squamous cell carcinoma	21 (37)	14 (48)
Large-cell carcinoma	2 (4)	1 (3)
Not otherwise specified or undifferentiated	7 (12)	2 (7)
Other	1 (2)	1 (3)
Median tumour size (range), mm	50 (15-155)	52 (15-166)
TNM classification, no (%)[b]		
T1N2M0	12 (21)	4 (14)
T2N2M0	16 (28)	7 (24)
T3N1M0	2 (4)	1 (3)
T3N2M0	13 (23)	5 (17)
T4N0M0	6 (11)	9 (31)
T4N1M0	8 (14)	3 (10)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; ITT, intention to treat; n, number; TNM, tumour-node-metastasis.

Note: The ITT population included all the patients who had undergone randomisation and received at least 1 cycle of neoadjuvant treatment. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

[a] ECOG PS scores range from 0 to 5, with higher scores indicating greater disability.

[b] TNM staging was based on the 8th edition of the AJCC Cancer Staging Manual. The reasons for T4 designation were a tumour size of greater than 7 cm (14 patients), invasion of great vessels (5 patients), mediastinal invasion (2

patients), separate tumour nodule in the same lobe of the primary tumour (2 patients), invasion of the chest wall (1 patient), invasion of the diaphragm (1 patient), and invasion of vertebral bodies (1 patient). The reasons for T3 designation were a tumour size of greater than 5 cm but less than 7 cm (14 patients), separate tumour nodule in the same lobe of the primary tumour (5 patients), and invasion of the parietal pleura (2 patients). Among the patients with T3N1M0 classification, the reasons for T3 designation were a tumour size of greater than 5 cm but less than 7 cm (2 patients) and separate tumour nodule in the same lobe of the primary tumour (1 patient). N2 status was further confirmed by means of endobronchial ultrasound–guided bronchoscopy (31 patients), mediastinoscopy (4 patients), or transthoracic fine-needle aspiration (22 patients). The average number of stations sampled was 1.95 (range, 1-5).

Source: Provencio, Nadal (7)

10.2.3 KEYNOTE-671

Table 35. KEYNOTE-671: baseline characteristics (Reproduced from Table 10 of the CS appendices)

Age, median year (range)	63 (26-83)	64 (35-81)
Male, n (%)	279 (70.3)	284 (71.0)
Race or ethnic group, n (%)		
American Indian or Alaska Native	1 (0.3)	0
Asian	124 (31.2)	125 (31.2)
Black	6 (1.5)	10 (2.5)
Multiple	3 (0.8)	10 (2.5)
White	250 (63.0)	239 (59.8)
Missing data	13 (3.3)	16 (4.0)
Geographic region, n (%)		
East Asia	123 (31.0)	121 (30.2)
Other	274 (69.0)	279 (69.8)
ECOG PS score, n (%)		
0	253 (63.7)	246 (61.5)
1	144 (36.3)	154 (38.5)
Smoking status, n (%)		
Current smoker	96 (24.2)	103 (25.8)
Former smoker	247 (62.2)	250 (62.5)
Never smoked	54 (13.6)	47 (11.8)
Pathological stage at baseline, n (%)		
II	118 (29.7)	121 (30.2)
III	279 (70.3)	279 (69.8)
IIIA	217 (54.7)	225 (56.2)
IIIB	62 (15.6)	54 (13.5)
Histology, n (%)		
Non-squamous	226 (56.9)	227 (56.8)
Squamous	171 (43.1)	173 (43.2)
PD-L1 tumour proportion score, n (%)		

≥ 50%	132 (33.2)	134 (33.5)
< 50%	265 (66.8)	266 (66.5)
1%-49%	127 (32.0)	115 (28.8)
< 1%	138 (34.8)	151 (37.8)
EGFR mutation status, n (%)		
No	111 (28.0)	127 (31.8)
Yes	14 (3.5)	19 (4.8)
Unknown	272 (68.5)	254 (63.5)
ALK translocation status, n (%)		
No	104 (26.2)	133 (33.2)
Yes	12 (3.0)	9 (2.2)
Unknown	281 (70.8)	258 (64.5)

Abbreviations: ALK, anaplastic lymphoma kinase gene; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; n, number; PD-L1, programmed death-ligand 1

Source: Wakelee, Liberman (25)

BMJ TAG

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non–small cell lung cancer [ID6310]

EAG report addendum

October 2025

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 175635.

1 Summary

The External Assessment Group (EAG) produced this addendum to the EAG report to present its view on the clinical similarity of nivolumab and durvalumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment (perioperative nivolumab and perioperative durvalumab) for resectable non-small cell lung cancer (NSCLC) compared to perioperative durvalumab and provide cost-comparison results for a scenario analysis of nivolumab versus durvalumab. The EAG notes that the company did not present results for nivolumab versus durvalumab in the company submission. However, during clarification the EAG requested the company included durvalumab in indirect treatment comparisons (ITCs) to enable a comparison of nivolumab versus durvalumab. These ITCs and their results are discussed in Section 2.1 below. In addition, similar to in the EAG report for the comparison of nivolumab versus pembrolizumab, the EAG has produced point-and-density plots for the comparison of nivolumab versus durvalumab (Section 2.2). The EAG also presents the results of the cost comparison scenario analysis for nivolumab versus durvalumab in Section 4, along with scenario analysis using the EAG's preferred assumptions.

Durvalumab has a slightly different mechanism of action to nivolumab as durvalumab selectively blocks the interaction of PD-L1 with PD-1 and CD80, whereas nivolumab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2. However, both drugs would potentially be considered for use at the same point in the treatment pathway for non-small cell lung cancer (NSCLC).

The EAG notes the [redacted] between perioperative nivolumab and perioperative durvalumab for [redacted] in the ITCs presented by the company. However, the EAG also notes that the hazard ratios (HRs) from the ITCs for EFS and OS [redacted] Given the EAG's concerns regarding the reliability of the results from the company's multilevel network meta-regressions (ML-NMRs) detailed in the EAG report, the EAG considers the results from the traditional Bayesian network meta-analyses (NMAs) and fractional polynomial (FP)–NMAs excluding NADIM-II may be the most reliable sources of efficacy estimates for perioperative nivolumab versus perioperative durvalumab. The EAG notes that in the analyses for OS the 95% credible intervals (95% CrIs) [redacted]

[redacted]

The EAG is not confident that the results from the ITCs are sufficient to conclude that clinical similarity has been demonstrated between perioperative nivolumab and perioperative durvalumab, particularly [redacted] The EAG's conclusion is further supported by

[redacted]

2 Summary of the EAG's critique of clinical effectiveness evidence

Due to the absence of head-to-head trial data comparing perioperative nivolumab with perioperative durvalumab, an indirect treatment comparison (ITC) is needed. As discussed in the External Assessment Group (EAG) report, the EAG considers the key nivolumab trial of relevance to the National Institute for Health and Care Excellence (NICE) final scope[1] to be CheckMate-77T.[2] The EAG notes that the key trial of durvalumab in TA1030[3] was the AEGEAN trial[4] and this trial was also identified in the company's systematic literature review (SLR) as being the only relevant trial for the comparison of perioperative durvalumab versus chemotherapy in the company's network meta-analysis (NMA) report. As mentioned in Section 1, the company did not present results for nivolumab versus durvalumab in the company submission but results from ITCs using CheckMate-77T and AEGEAN were provided in the company's response to clarification questions. These ITCs and their results are discussed in Section 2.1

2.1 Critique of the indirect treatment comparisons

2.1.1 Critique of trials identified and included in the indirect treatment comparison

Based on the NICE final scope and the advice of clinical experts, the EAG notes that both perioperative pembrolizumab and perioperative durvalumab could be considered comparators for perioperative nivolumab. In the clarification questions, the EAG requested updated ITCs including only the three trials which were most relevant to the decision problem (CheckMate-77T, KEYNOTE-671[5] and AEGEAN). As discussed in the EAG report, the EAG prefers the exclusion of the NADIM-II study[6] from the ITCs due to concerns about its relevance to NHS clinical practice. The company's ITCs for nivolumab versus durvalumab therefore comprise of only the trials that the EAG considers to be most relevant to the decision problem. The EAG's critique in the EAG report focuses on the results from the comparison of nivolumab versus pembrolizumab (CheckMate-77T and KEYNOTE-671), whereas the critique in this addendum focusses only on the results from nivolumab versus durvalumab (CheckMate-77T and AEGEAN). A comparison of the CheckMate-77T and AEGEAN trials that have been included in the ITCs for perioperative nivolumab versus perioperative durvalumab, including trial design, treatments and doses, are presented in Table 1.

Table 1. Overview of CheckMate-77T and AEGEAN studies.

Study	Number of patients	Median follow-up (years)	Intervention and dose	Comparator
CheckMate-77T	461	3.4	Neoadjuvant treatment: • Nivolumab 360 mg every 3 weeks + standard of care chemotherapyfor up to 4 cycles Adjuvant treatment: • Nivolumab 480 mg every 4 weeks for up to 13 cycles (approximately 1 year)	Neoadjuvant treatment: • Placebo every 3 weeks + standard of care chemotherapyfor up to 4 cycles as neoadjuvant therapy followed by surgery Adjuvant treatment: • Placebo every 4 weeks for up to 13 cycles (approximately 1 year) after surgery
AEGEAN	740	2.2	Neoadjuvant treatment: • Durvalumab 1500 mg every 3 weeks for four cycles in combination with platinum-based chemotherapy Adjuvant treatment: • Durvalumab 1500 mg every 4 weeks for up to 12 cycles	Neoadjuvant treatment: • Placebo every 3 weeks for four cycles in combination with platinum-based chemotherapy Adjuvant treatment: • Placebo every 4 weeks for up to 12 cycles

Abbreviations: m, metres; mg, milligrams

Assessment of the quality of the evidence for the durvalumab trial (AEGEAN) is presented in Table 2. While there are limited concerns about the methods used for AEGEAN, it should be noted that, unlike CheckMate-77T, patients were included if they had confirmed epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations. However, following a protocol deviation, these patients were excluded from the efficacy analyses, and the modified intention to treat (mITT) population was instead used for analyses. The EAG notes that EGFR mutations and ALK translocations were not stratified for at randomisation in AEGEAN, thereby resulting in a breaking of randomisation for the mITT analyses. Despite this, baseline characteristics in the mITT population and the number of patients excluded from each trial arm (EGFR mutations: durvalumab n=26, placebo n=25; ALK translocations: durvalumab n=8, placebo n=3) were similar. However, the breaking of randomisation should be considered when comparing the results for the two trials.

While there were some differences between the baseline characteristics of the two trials, such as a higher percentage of white patients and lower percentage of Asian patients in CheckMate-77T, the EAG's clinical experts did not consider these to be important treatment-effect modifiers. Other

differences, such as the percentage of never smokers (CheckMate-77T: 7.4% for nivolumab, 11.6% for placebo; AEGEAN: 13.9% for durvalumab, 15.0% for placebo), may have more of an impact on the effects of treatment and should therefore be considered when interpreting the results.

The EAG notes that both trials used similar perioperative treatment regimens, but adjuvant treatment was provided for up to 13 cycles in CheckMate-77T, whereas in AEGEAN it was limited to up to 12 cycles. In both trials, patients could receive either cisplatin or carboplatin as neoadjuvant chemotherapy. A similar percentage of patients received each type of chemotherapy, with carboplatin used most commonly (72.9% of nivolumab patients and 77.6% of placebo patients received carboplatin in CheckMate-77T, compared to 72.7% of durvalumab patients and 74.2% of placebo patients in AEGEAN). However, it should be noted that the percentages for AEGEAN are based on the planned neoadjuvant platinum agent for each patient, rather than the platinum agent actually received during the trial.

In terms of outcomes, both CheckMate-77T and AEGEAN used EFS assessed using blinded independent central review (BICR) as their primary EFS outcome. The EAG notes that the company identified investigator-assessed EFS (EFS-INV) from the European Public Assessment Report (EPAR) of the AEGEAN trial[7]

[redacted] The EAG notes that these data for EFS-INV were from interim analysis (IA) 1 of AEGEAN (10 November 2022). The EFS-BICR data from IA1 had a median duration of follow-up of 11.7 months (censored patients) and 31.9% data maturity (equivalent data for EFS-INV not reported). In contrast, the data used in the company's ITCs are for EFS-BICR from IA2 (data cut off 10 May 2024) with a median follow-up of 25.9 months (censored patients) and EFS-BICR data maturity reported as 39.1% with median EFS not reached in the durvalumab trial arm. As discussed in the EAG report, the EAG considers EFS-BICR to be the preferred outcome assessment for EFS, and the EAG also prefers the use of the latest available data. The EAG thus recommends caution in interpreting the results of EFS-INV for the comparison of nivolumab versus durvalumab and considers the results from EFS-BICR likely to be more reliable. Nevertheless, given the preference for EFS-INV in the EAG report for the comparison of nivolumab versus pembrolizumab, the EAG discusses the results for both EFS-BICR and EFS-INV for the comparison of nivolumab versus durvalumab in this addendum.

Median follow-up for OS in AEGEAN was 33.6 months, but the EAG notes that median OS was reached in the durvalumab arm at the data-cut off (10 May 2024) used in the ITCs presented in this report.

OS was a key secondary endpoint for both trials. While the definition of OS used in each trial is not a concern, the EAG notes that the OS data reported for CheckMate-77T is [redacted]. As such, while there are no concerns about the assessment of survival, [redacted]

Median follow-up in CheckMate-77T for the data cut off used in the ITCs was [redacted]

Table 2. EAG's summary of the design, conduct and analysis of AEGEAN

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Heymach *et al*. 2023	**Appropriate** Patients were randomised using 1:1 randomisation. Randomisation was stratified based on disease stage (II or III) and programmed death ligand 1 (PD-L1) expression (≥1% or <1%).
Concealment of treatment allocation	Heymach *et al*. 2023	**Appropriate** The study was double-blind, and primary endpoints were assessed centrally by individuals who were blinded to treatment allocation.
Eligibility criteria	Heymach *et al*. 2023	**Appropriate** Males and females aged ≥ 18 years Newly diagnosed, previously untreated, histologically or cytologically documented, resectable NSCLC (stage IIA to stage IIIB [N2 node stage] disease, according to the eighth edition of the *AJCC Cancer Staging Manual)* Planned surgical treatment with lobectomy, sleeve resection or bilobectomy Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 Estimated life expectancy of at least 12 weeks Documented tumour PD-L1 status and the presence of at least one lesion that qualified as a target lesion according to [RECIST], version 1.1.
Baseline characteristics	Heymach *et al*. 2023	**Appropriate**

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
		Most baseline characteristics were balanced across arms, with marginal differences for some characteristics such as the percentage of Asian patients (39% for durvalumab, 44% for placebo) and patients with squamous tumours (46% for durvalumab, 51% for placebo).
Dropouts	Heymach *et al*. 2023	**Unclear** Limited information provided about patient dropouts.
Statistical analysis		
Sample size and power	Heymach *et al*. 2023	**Appropriate** The interim analysis was designed to have a 55% power to detect a between-group difference of 12 percentage points at a two-sided significance level of 0.008% (based on a modified intention to-treat population of 400 patients) and a HR for disease progression, recurrence, or death of 0.69 with a two-sided significance level of 0.665% (based on 740 patients in the modified intention-to-treat population with 224 events). A total of 802 patients were randomised to study treatments.
Handling of missing data	Heymach *et al*. 2023	**Unclear** No information is provided about missing data.
Outcome assessment	Heymach *et al*. 2023	**Appropriate** Clinical response outcomes were assessed using measures that are commonly used in practice or research.

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern cooperative Oncology Group; NSCLC, non-small cell lung cancer; PD-L1, Programmed death-ligand 1; RECIST, response criteria in solid tumors

2.1.2 Critique of the methods used for the indirect treatment comparison

The company conducted ITCs to compare perioperative nivolumab with perioperative durvalumab with the methods used based on ITCs that were performed as part of a global project assessing treatment efficacy across multiple treatments of patients with stage II-IIIB resectable non-metastatic NSCLC. The company reported results from three different methods of analysis in response to clarification questions:

1) a traditional Bayesian network meta-analysis (NMA);
2) a fractional polynomial (FP)–NMA, which relaxed the proportional hazards (PH) assumption required by traditional Bayesian NMA; and

3) a multilevel network meta-regression (ML-NMR) to generate estimates of relative effect adjusted to the population in CheckMate-77T.

The primary outcomes of interest in the company's ITCs were EFS and OS. The EAG notes that all the analyses reported by the company were conducted using the statistical software R.[8] For the NMA, the files provided by the company allowed analyses to be run, but the EAG does not consider the code provided to be sufficient to produce the required outputs for the EAG to fully validate the company's results or model fit. The EAG has therefore conducted independent validation of the company's Bayesian NMA using the Bucher ITC method for the analyses of EFS and OS and obtained similar results to the company. However, the EAG was unable to conduct its own FP-NMAs due to time constraints and was unable to validate the company's FP-NMA analyses due to time constraints and the volume of information (e.g. [redacted] from the company's code). The EAG also considers there to be a lack of detail provided to explain the FP-NMA code and the output files produced by it. In addition, the EAG did not have access to the individual patient-level data (IPD) required to undertake the validation of the ML-NMR.

The CS was accompanied by an NMA report that provided additional details on the company's ITCs. In the NMA report, it was explained that the proportional hazards assumption within each trial was evaluated through a visual inspection of the Kaplan-Meier (KM) data, log cumulative hazard plots, Schoenfeld residuals, and Grambsch-Therneau tests. In the CS, the company reported that the PH assumption was not rejected in CheckMate-77T, and visual inspections did not suggest obvious deviations. The EAG does not consider there to be sufficient evidence from the assessments of PH presented by the company to reject the assumption of PH for either CheckMate-77T or AEGEAN.

The EAG notes that the company reported results for the ITCs from [redacted] effects models, which the EAG considers to be reasonable given [redacted]. In addition, the EAG notes that the results from the company ITCs for EFS for perioperative nivolumab versus perioperative durvalumab are all for EFS-BICR with the exception of the results from a Bucher ITC for EFS-INV. As discussed earlier, the EAG considers EFS-BICR to be the most robust assessment of EFS and notes that it uses the latest data cut from both CheckMate-77T and AEGEAN.

2.1.3 Traditional Bayesian network meta-analysis

In the traditional Bayesian NMA, the HR for

EFS [redacted]

[redacted] Table 3 [redacted] Table 3 [redacted]

As detailed above, the EAG also reports the results for EFS-INV for perioperative nivolumab versus perioperative durvalumab for consistency with the outcomes reported in the EAG report. EFS-INV was not an outcome in the company's Bayesian NMA and therefore the EAG reports only the result from Bucher ITCs. The EAG considers the results of EFS-INV [redacted] the EAG considers the results for EFS-BICR to be more reliable as they relate to the latest data cut from AEGEAN.

Table 3. Traditional Bayesian NMA results for EFS and OS from the company's analyses of perioperative nivolumab versus perioperative durvalumab

Outcome	Network excluding NADIM-II Fixed effect model HR (95% CrI)
EFS-BICR	[redacted]
EFS-INV	[redacted]
OS	[redacted]

[redacted]

Abbreviations: CrI, credible interval; BICR, blinded independent central review; EFS, event-free survival; HR, hazard ratio; IA, interim analysis; INV, investigator-assessed; NMA, network meta-analysis.

2.1.4 Fractional polynomial network meta-analysis

The company conducted an FP-NMA to allow for non-linear modelling of treatment effects over time (time-varying HRs) for the outcomes of EFS and OS. The EAG notes that the FP-NMA is not dependent on a PH assumption holding [redacted]. Also, as noted in Section 2.1.2, the EAG was unable to validate the results from the company's FP-NMA.

2.1.4.1 FP-NMA EFS results

For the FP-NMA for EFS, the company concluded that the best-fitting non-PH model was a first-order Weibull-based fractional polynomial with powers [redacted], where treatment effects were applied to the first and third terms. However, the EAG considers the model to be a second-order FP model rather than first-order given it has two powers defined.

The EAG notes that the EFS HRs of perioperative nivolumab relative to perioperative durvalumab [redacted] (Table 4). The FP-NMA results for the comparison between perioperative nivolumab and perioperative durvalumab had a HR of [redacted] Table 4 [redacted] EAG notes that the HRs for the analysis of EFS [redacted] Table 4 [redacted]

Table 4. Event-free survival hazard ratios of perioperative nivolumab versus perioperative durvalumab over time in the fractional polynomial network meta-analysis (Adapted from Table 18 of the company response to clarification questions)

Time	Network excluding NADIM-II HR (95% CrI)
3	[redacted]
6	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]
30	[redacted]
36	[redacted]
42	[redacted]
48	[redacted]
54	[redacted]
60	[redacted]
[redacted]	

2.1.4.2 FP-NMA OS results

For the FP-NMA including AEGEAN, the company reported that the best-fitting non-PH model was a first-order fractional polynomial with powers [redacted], where treatment effects were applied to the first and second terms. However, the EAG considers the model is a second-order FP model rather than first-order given it has two powers defined.

The EAG notes that the OS HRs of perioperative nivolumab relative to perioperative durvalumab from the FP-NMAs [redacted] months (Table 5). The EAG notes that median follow-up in CheckMate-77T and AEGEAN for data used in this analysis was [redacted] and 33.6 months, respectively. The EAG thus considers that the HRs at later time points (i.e. [redacted]) should be interpreted with caution due to censoring and limited follow-up.

With respect to the comparison between perioperative nivolumab and perioperative durvalumab, in the FP-NMA for OS the HRs [redacted]

Table 5. Overall survival hazard ratios of perioperative nivolumab versus perioperative durvalumab over time in the fractional polynomial network meta-analysis (Adapted from Table 19 of the company response to clarification questions)

Time	Network excluding NADIM-II Fixed effect model HR (95% CrI)
3	[redacted]
6	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]
30	[redacted]
36	[redacted]
42	[redacted]
48	[redacted]
54	[redacted]
60	[redacted]

[redacted]

2.1.5 Multilevel network meta-regression

The company conducted an ML-NMR with limited adjustments for imbalances in patient populations across trials in the network. The company reported that the characteristics for adjustment used in the ML-NMR were identified using clinical input, evidence collected from an SLR, and external evidence identified in advanced NSCLC populations. Disease stage was identified as a prognostic factor and PD-L1 expression level was identified as an effect modifier and therefore both were adjusted for in the company's ML-NMR using the population characteristics in CheckMate-77T. The EAG considers it to be unclear whether [redacted] was also included as an adjustment factor in the company's original ML-NMR [redacted]

The EAG considers that adjusting for all potential prognostic and treatment effect modifiers (and so all available baseline characteristics) would have been a more robust approach, thus requested that the company conducted a fully adjusted ML-NMR analysis in their clarification questions. The results of the fully adjusted ML-NMR are discussed below alongside the results of the company's ML-MNR with adjustment for the limited set of characteristics.

The company reported that the fully adjusted analysis included covariate adjustment for all key baseline characteristics reported across trials with the exception of age. Prognostic factors were: disease stage, ECOG performance status, sex, region, smoking status, histology, and PD-L1 expression level; and treatment effect modifiers were: PD-L1 expression level, disease stage, and region. The company also reported that age was very similar across trials (median age ranged from 63 to 66 years in AEGEAN, KEYNOTE-671, CheckMate-77T, and NADIM-II) and was well-balanced across trial arms. The EAG thus considers the omission of adjustment for age in the company's ML-NMR to be unlikely to have a clinically meaningful impact on the overall results.

2.1.5.1 ML-NMR EFS results

The company reported that nine parametric forms (exponential, accelerated failure time Weibull, proportional hazards Weibull, Gompertz, lognormal, loglogistic, gamma, generalized gamma and M-spline) were considered. Furthermore, the company reported that model fit was assessed using a network of trials which comprised a wider network than that included in the final ML-NMR in the company submission. The model fit in this wider network was assessed using the model fit statistics,

visual inspection, and clinical plausibility with the 4-knot M-spline model considered to be the top-fitting M-spline model. The EAG notes that the 4-knot M-spline non-PH model that had the best fit did not adequately converge despite implementation updates to address non-convergence and therefore the next best-fitting model was selected. This was the 4-knot PH M-spline model, despite concerns that it potentially overfit to the tails of the KM EFS data. The EAG is concerned that the 4-knot PH M-spline model does not appear to be a good visual fit for the CheckMate-77T K-M data given that IPD from this trial is used in the ML-NMR (i.e. the ML-NMR does not appear to predict the underlying data very well, which the EAG considers to be a potential symptom of model misspecification). The EAG is also unclear whether adjustments were made to the model specification for the analyses of EFS as detailed in the NMA report Section 12.1. In the event adjustments have been applied, the EAG considers there to be a lack of detail on the adjustments (e.g. which priors were adjusted, how were these priors selected for adjustment, what was the evidence base for the informed priors, what was the justification for the *post hoc* adjustment). The EAG is therefore concerned about the reliability of the results from the company's ML-NMRs for EFS.

The ML-NMR results for EFS for the comparison between perioperative nivolumab and perioperative durvalumab [redacted] Table 6 [redacted] Table 6 [redacted] Table 6. Event-free survival hazard ratios of perioperative nivolumab versus perioperative durvalumab over time in the multilevel network meta-regression (adapted from Table 14 of the company response to clarification questions)

Time	Network excluding NADIM-II HR (95% CrI)	Network excluding NADIM-II and with all covariates HR (95% CrI)
6	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]
36	[redacted]	[redacted]
42	[redacted]	[redacted]
48	[redacted]	[redacted]
54	[redacted]	[redacted]

60	[redacted]	[redacted]
[redacted]		

2.1.5.2 ML-NMR OS results

For the ML-NMR analysis of OS, the company's preferred model was [redacted] model. The EAG notes that the same model was used for all of the company's ML-NMR analyses of OS [redacted]. As noted earlier, the EAG did not have access to the necessary data to enable validation of the results from the company's ML-NMR. The EAG reiterates its concerns from the EAG report, that the EAG has concerns about the relatively poor visual fit of the 1-knot M-spline PH ML-NMR to the CheckMate-77T K-M data given that IPD from this trial is used in the ML-NMR (i.e. the ML-NMR does not appear to predict the underlying data very well, which the EAG considers to be a potential symptom of model misspecification).

The HRs from the ML-NMR for the comparison between perioperative nivolumab and perioperative durvalumab [redacted] Table 7 [redacted] Table 7 [redacted] Table 7. Overall survival hazard ratios of perioperative nivolumab versus perioperative durvalumab over time in the multilevel network meta-regression (adapted from Table 14 of the company response to clarification questions)

Time	Network excluding NADIM-II HR (95% CrI)	Network excluding NADIM-II and with all covariates HR (95% CrI)
6	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]
36	[redacted]	[redacted]
42	[redacted]	[redacted]
48	[redacted]	[redacted]
54	[redacted]	[redacted]

60	[redacted]	[redacted]
[redacted]		

2.2 Additional work on clinical effectiveness undertaken by the EAG

2.2.1 EAG's point-and-density plots

The EAG has conducted Bayesian NMAs using R (v4.2.0) to generate point-and-density plots for the comparison of perioperative nivolumab versus perioperative durvalumab. Full details of the methods used are provided in Section 4.5.2 of the EAG report. In addition, to the point-and-density plots, in the absence of a defined non-inferiority margin (NIM) for EFS and OS, the EAG also presents the estimated NIM that would be required in order for there to be a 95% probability that nivolumab is non-inferior to durvalumab for each outcome based on the corresponding empirical cumulative density function (ECDF) for each comparison.

2.2.1.1 Point-and-density plot results for EFS

As shown by the point-and-density plot (Figure 1),
[redacted] In terms of EFS-BICR, using the latest available data-cut for AEGEAN with data available for this outcome, the probability of non-inferiority is [redacted] Figure 2[redacted]

Based on the ECDF, the EAG estimates that the hypothetical NIM that would be required in order for there to be a 95% probability that nivolumab is non-inferior to durvalumab for EFS-BICR is
[redacted]

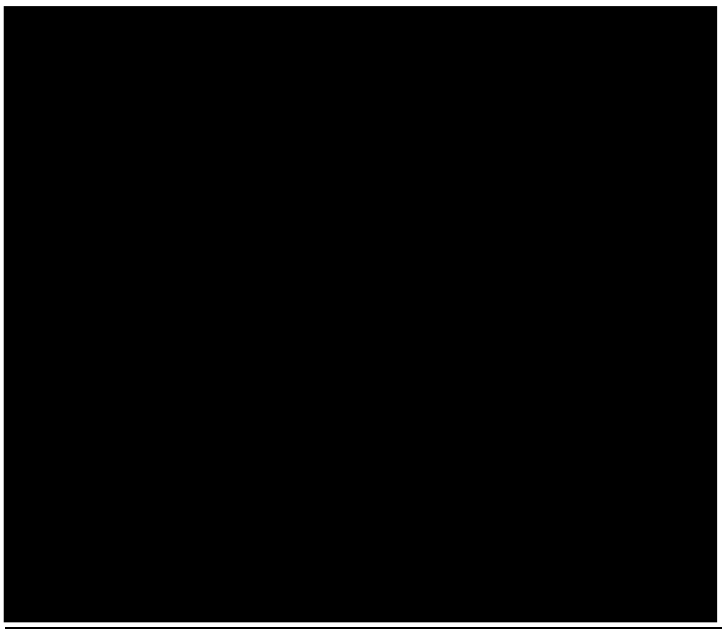
For EFS-INV, the hypothetical NIM that would be required in order for there to be a 95% probability that nivolumab is non-inferior to durvalumab for EFS-BICR is
[redacted]

As discussed previously, the EAG considers the findings from the EFS-INV analysis to potentially be unreliable, and the EAG considers the use of the latest data cut for EFS to be preferred. Based on the available data, the EAG therefore prefers the use of EFS-BICR as it has a later data cut than EFS-INV.

In addition, EFS-BICR could be considered more methodologically robust due to the blinding of the outcome assessment.

Figure 1. Point-and-density plot for the comparison of perioperative nivolumab to perioperative durvalumab for EFS-INV.

Figure 2. Point-and-density plot for the comparison of perioperative nivolumab to perioperative durvalumab for EFS-BICR



2.2.1.2 *Point-and-density plot results for OS*

The point-and-density plot for OS (Figure 3)

[redacted]

Based on the ECDF, the EAG estimates that the hypothetical NIM that would be required in order for there to be a 95% probability that nivolumab is non-inferior to durvalumab for OS is

[redacted]

Figure 3. Point-and-density plot for the comparison of perioperative nivolumab to perioperative durvalumab for OS

2.3 Adverse effects

The most common treatment-related AEs (occurring in ≥15% of patients) with nivolumab were anaemia, nausea, alopecia, constipation, fatigue and decreased neutrophil count (Table 8). A similar percentage of patients in each arm experienced treatment-related AEs, few of which were classed as Grade 3-4.

[redacted]

[redacted] (a difference of [redacted] for any grade AE and [redacted] for Grade 3-4 AEs). The only treatment-related AE reported more commonly with placebo than nivolumab was [redacted] which was experienced by [redacted] of placebo patients compared to [redacted] with nivolumab.

AEGEAN reported a wider range of common treatment-related AEs associated with durvalumab than were reported for nivolumab in CheckMate-77T. However, the percentage of patients experiencing an AE is not directly comparable, with AEGEAN reporting common AEs as those occurring in ≥5% of patients, compared to the ≥15% threshold reported for CheckMate-77T.

[redacted] (Table 8). For treatment-related AEs of any grade, [redacted] were reported more commonly with nivolumab than durvalumab. However, as results were not separated by immunotherapy- or chemotherapy-related AEs it is difficult to establish if this difference was due to a response to nivolumab, or whether it instead reflects the different chemotherapy regimens used in the trials. Differences between nivolumab and durvalumab for Grade 3-4 treatment-related AEs were [redacted] and there were [redacted]. Advice from the EAG's clinical experts also suggested that there are no major differences in safety profiles expected between perioperative nivolumab and perioperative durvalumab.

Table 8. Most common treatment-related AEs reported in the CheckMate-77T and AEGEAN trials (adapted from Table 8.1.1-1 in the CSR)

Adverse event	CheckMate-77T*		KEYNOTE-671†	
	Nivolumab (n=228)	Placebo (n=230)	Durvalumab (n=401)	Placebo (n=398)
Any grade treatment-related AEs				
[redacted]	[redacted]	[redacted]	105 (26.2)	96 (24.1)
[redacted]	[redacted]	[redacted]	86 (21.4)	96 (24.1)
[redacted]	[redacted]	[redacted]	66 (16.5)	58 (14.6)
[redacted]	[redacted]	[redacted]	44 (11.0)	50 (12.6)
[redacted]	[redacted]	[redacted]	42 (10.5)	36 (9.0)
[redacted]	[redacted]	[redacted]	62 (15.5)	56 (14.1)
Grade 3-4 treatment-related AEs				
[redacted]	[redacted]	[redacted]	18 (4.5)	20 (5.0)
[redacted]	[redacted]	[redacted]	1 (0.2)	1 (0.3)

[redacted]	[redacted]	[redacted]	0 (0)	1 (0.3)
[redacted]	[redacted]	[redacted]	0 (0)	0 (0)
[redacted]	[redacted]	[redacted]	0 (0)	0 (0)
[redacted]	[redacted]	[redacted]	38 (9.5)	42 (10.6)

Abbreviations: AE, adverse event; n, number

* Treatment-related AEs occurring in ≥15% of patients

† Treatment-related AEs occurring in ≥5% of patients

2.4 Conclusions of the clinical effectiveness section

No trials made direct head-to-head comparisons between perioperative nivolumab and perioperative durvalumab, therefore, ITCs have been used to compare the two treatments.

Overall, the EAG does not consider there to be sufficient evidence from [redacted] The EAG [redacted] for the comparison of perioperative nivolumab and perioperative durvalumab.

In terms of the FP-NMAs and the ML-NMRs, the EAG is unable to confirm the replicability of the results from either method of analysis. For the ML-NMRs, the EAG is further concerned with the reliability of the results [redacted] The EAG also notes a lack of adjustment for all potential prognostic factors and treatment effect modifiers in the company's base case ML-MNR and considers the analyses with adjustment for all characteristics to be preferred.

The EAG, considers that using EFS-BICR, as it is reported from a later data cut, in the ITCs is the preferred assessment for analyses of EFS, and recommends caution in drawing conclusions from the results of EFS-INV.

The results from the company's three ITCs excluding NADIM-II for EFS and OS [redacted] between perioperative nivolumab and perioperative durvalumab. [redacted]

[redacted]

The EAG conducted analyses to generate point-and-density plots for the EFS and OS results from standard NMA of data from CheckMate-77T and AEGEAN. The company did not report a NIM or MCID for either EFS or OS and therefore the EAG has used a threshold of 0 on the log-scale (the equivalent of a HR of 1), which may represent a conservative threshold by which to assess non-inferiority. The findings from the EAG's analyses indicate [redacted] of non-inferiority for perioperative nivolumab compared to perioperative durvalumab for the outcomes of EFS-BICR and OS. In addition, in the absence of a specified NIM for EFS and OS, the EAG estimated what the upper limit of that margin would need to be to give sufficient certainty of clinical similarity.

[redacted]

Overall, [redacted], and [redacted], the EAG [redacted] between perioperative nivolumab and perioperative durvalumab.

3 Summary of the cost comparison scenario analysis

3.1 Cost assumptions

The costing assumptions in the EAG's scenario analysis that include durvalumab as a comparator are the same as those in the company's submission (described in Section 5.1 of the EAG report). Namely, the assumption that adverse events; health care resource use; subsequent treatments; and end of life costs would be similar across the two treatments, leading to their exclusion from the analysis.

3.2 Acquisition costs

The EAG has produced a confidential appendix to the EAG report, which takes into account the confidential price for durvalumab. The confidential appendix includes scenario analyses and the company and EAG's base case results.

Table 9 presents the estimated acquisition costs of nivolumab and durvalumab for the cost comparison. The dosing and regimen for nivolumab was informed using CheckMate-77T, reflecting the company's base case analysis, with the durvalumab dosing and regimen being informed by NICE TA1030, which evaluated durvalumab for the treatment of perioperative resectable non–small cell lung cancer. In AEGEAN, durvalumab's pivotal trial, neo-adjuvant durvalumab was administered intravenously at a dose of 1,500 mg with platinum-based chemotherapy every three weeks for four cycles. Post-surgery, durvalumab was administered as a monotherapy at the same dose, for a maximum of 12 cycles administered every four weeks.

As outlined in Table 9, relative to durvalumab, nivolumab is the less costly treatment in terms of treatment acquisition costs.

Table 9. Treatment acquisition costs

	Perioperative nivolumab		Perioperative durvalumab	
	Neoadjuvant	Adjuvant	Neoadjuvant	Adjuvant
Pharmaceutical formulation	10 mg/mL		500 mg	
Acquisition cost	£439 per vial		£2,466 per vial	
Method of administration	IV			
Doses	360 mg	480 mg	1,500 mg	1,500 mg
Dosing frequency	Q3W	Q4W	Q3W	Q6W
Average length of a course of treatment	3 weeks	4 weeks	3 weeks	4 weeks

Average cost of a course of treatment	£3,951	£5,268	£7,398	£7,398
Number of repeat courses of treatment	4	13	4	12
Duration of treatment*	12 weeks	52 weeks	12 weeks	48 weeks
Total cost over treatment duration	£15,804	£68,484	£29,592	£88,776
Total cost of perioperative regimen	£84,288		£118,368	

Abbreviations: IV, Intravenous; QxW, every x weeks.

*Includes length of course of final treatment after treatment administration

3.3 Administration costs

Table 10 presents the administration costs included in the company's base case cost comparison analysis. As described in detail in Section 5.4 of the EAG report, the EAG considers that the healthcare resource groups (HRG) cost from the National Cost Collection for the NHS (NCC) are more appropriate than the Outpatient Procedure (OPROC) costs used by the company, with TA1017 also using the HRG costs.

Table 11 presents the administration costs across the different costing approaches. Included in the EAG's preferred assumptions are the use of code SB15Z to cost subsequent treatment administrations, given codes SB13Z and SB12Z used by the company are specific to first attendances (Table 11).

Table 10. Administration frequencies and costs

	Nivolumab		Durvalumab	
	Neoadjuvant	Adjuvant	Neoadjuvant	Adjuvant
Source	National Cost Collection for the NHS (2024)[9]			
Cost sheet (service code)	Outpatient procedures (Medical oncology service and Clinical Oncology Service weighted costs)			
Cost code	SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance	SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance	SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance	SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance
Weighted costs	£190.69	£138.10	£190.69	£138.10
Number of units	4	13	4	12
Cost over the full-time horizon	£762.76	£1,795.34	£762.76	£1,657.23

Abbreviations: NHS, National Health Service

Table 11. Administration costs and sources

	Company submission (£)	TA1017 (£)	EAG preferred (£)
SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance	138	287	394
SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance	191	354	509
Source	NCC 2023/2024	NCC 2020/2021	NCC 2023/2024
Sheet	OPROC	HRG	HRG

Abbreviations: HRG, Healthcare Resource Group; OPROC, Outpatient procedures; NCC, National Cost Collection for the NHS.

4 EAG preferred assumptions and scenario analysis results

4.1 EAG's preferred assumptions

Table 12 presents the incremental and cumulative impact of the EAG's preferred assumptions. As outlined, nivolumab was found to be cost-saving relative to durvalumab across all scenarios when assuming treatment effects to be similar.

Table 12. EAG preferred assumptions

Assumption	Nivolumab total costs (£)	Durvalumab total costs (£)	Independent incremental difference in costs (£)	Cumulative incremental difference in costs (£)
Company preferred assumptions	86,846.10	120,788.00	-33,941.90	-
HRG administration costs	91,448.01	125,133.85	-33,685.83	-33,685.83
Costing subsequent administration using cost code SB15Z	87,964.90	121,821.69	-33,856.79	-33,649.76

Abbreviations: HRG, Healthcare Resource Group.

4.2 Scenario outcomes

Table 13 and Table 14 present the scenario analysis outcomes comparing nivolumab to durvalumab under the company's and EAG's preferred assumptions.

Table 13. Scenario analysis outcomes with company preferred assumptions

Interventions	Acquisition costs (£)	Administration costs (£)	Total Costs (£)	Incremental costs (£)
Nivolumab	84,288.00	2,558.10	86,846.10	-
Durvalumab	118,368.00	2,420.00	120,788.00	-33,941.90

Table 14. Scenario analysis outcomes with EAG preferred assumptions

Interventions	Acquisition costs (£)	Administration costs (£)	Total Costs (£)	Incremental costs (£)
Nivolumab	84,288.00	7,356.75	91,644.75	-
Durvalumab	118,368.00	6,926.51	125,294.51	-33,649.76

Abbreviations: External Assessment Group

5 References

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Cost Comparison Appraisal

Nivolumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6310]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 6 October 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Insufficient information to validate the analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 9 (addendum): *"The EAG notes that all the analyses reported by the company were conducted using the statistical software R and, despite requests, the EAG did not receive the necessary files to validate any of the company's analyses. … The EAG was unable to conduct its own FP-NMAs due to time constraints and was unable to validate the company's FP-NMA analyses due to the missing files."*	Despite the company providing all the required files for both the Bayesian NMA and FP-NMA, the EAG was unable to conduct its own FP-NMAs due to time constraints and was unable to validate the company's FP-NMA analyses.	This correction is important because it clarifies that the company provided complete and sufficient materials for validation of both the Bayesian NMA and FP-NMA. The EAG's statement implies a lack of transparency or withholding of information, which is inaccurate and could undermine confidence in the robustness of the analyses. A statistician not involved in the conduct of analyses was able to generate results from all models using only the information provided to the EAG. For the Bayesian NMA, a file reference issue in the R code was corrected and resubmitted during the second round of clarifications. For the FP-NMA, the full set of R scripts and JAGS code was provided (folder labelled "CODE," containing the "R" and "jags"	Thank you for highlighting this error. The EAG report and addendum have been updated to acknowledge that the company provided files for the NMA and FP-NMA but the EAG was unable to fully validate the company's analyses.

		subfolders). These files allow reproduction of the analysis end-to-end. Only figure-generating scripts were not included, as these are not required for validating model results.	

Issue 2 Reliability of the ML-NMR evidence

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14 & Page 84-85 (numbered for cross-referencing against provided justification): *"The validity of the ML-NMR results due to:* 1. *The lack of adjustment for all potential prognostic factors and treatment effect modifiers in the company's base case ML-MNR;* 2. *The lack of convergence in the model for EFS;* 3. *The poor fit of the PH 4-Knot M-spline model for EFS to the*	The company disagrees that the ML-NMR lacks validity and requests a complete removal of this text	The disputed text presents a misleading description of the company's ML-NMR work. Retaining this text risks biasing the committee against the only approach that properly adjusts for cross-trial covariate differences. On this basis, we respectfully request complete removal of the section. If retained, it should at minimum be reframed to reflect that the presented ML-NMR results are appropriate and relevant for decision-making. The justification for rebuttal of each of the points made by the EAG is provided below: 1. The company provided both base case and fully adjusted	Thank you for highlighting this. The EAG report has been amended to reflect that the EAG considers there to be a lack of clarity on the methods for the ML-NMR and the EAG remains concerned about the model fit. The EAG has removed the text relating to the lack of adjustment for all prognostic factors in the company's ML-NMR from the executive summary and Section 8 of the EAG report, and the text relating

underlying KM data, particularly for Check-Mate-77T; 4. *The use of a wider network to make the model selection than that used to run the final model for EFS;* 5. *The lack of detail on the methods for OS"*		ML-NMR results in our response to clarification questions. These analyses were conducted on the set of studies that the EAG deemed relevant. Results demonstrated robustness of the base case to inclusion of additional covariates, confirming that conclusions do not depend on the choice of adjustment set. 2. The report's wording infers a general convergence problem with ML-NMR, which is inaccurate. Only the single "top-fitting" specification did not converge. 3. The selected PH 4-Knot M-spline model for EFS was the best among the converged alternatives; the difference in LOOIC relative to the non-converged model (ΔLOOIC = 8) is not decision-relevant. Furthermore, rejecting the ML-NMR results on visual grounds is inconsistent with NICE DSU guidance, which prioritizes	to the OS methods following the additional information provided by the company. Based on the available information, the EAG is unclear whether adjustments were made to the model specification for the analyses of EFS as detailed in the NMA report Section 12.1. In the event adjustments have been applied, the EAG considers there to be a lack of detail on the adjustments (e.g. which priors were adjusted, how were these priors selected for adjustment, what was the evidence base for the informed priors, what was the justification for the *post hoc* adjustment?). The EAG acknowledges that the company has chosen the best fitting

		parsimony, convergence, and predictive adequacy. 4. Using a wider network for selection of the functional form for time is appropriate, particularly in the context of ML-NMR where model fitting is computationally intensive. There were no identified clinical or methodological considerations suggesting that model selection on the wider network was inappropriate, and importantly the EAG has not identified any such concerns. Knot placement was informed solely by IPD data, meaning the choice of baseline hazard specification would have remained consistent irrespective of which network was used. The same methods and model selection principles were applied consistently to both EFS and OS. The EAG's assessment of insufficient methodological detail for OS is not supported; methods were thoroughly	model of the options available, but the EAG considers this to be a relative assessment of goodness of fit rather than being indicative of a good-fitting model (in absolute terms). The EAG considers that a visual inspection of how well the selected model for the ML-NMR fits the KM data for a trial supplying IPD is a useful validation tool. The EAG considers that a poor visual fit is a potential symptom of model misspecification. While the EAG appreciates that visual inspection is not a quantitative assessment the EAG considers it standard practice in survival analysis. The EAG remains concerned about the visual fit for EFS and OS for CheckMate-77T and the EAG considers the results from the ML-NMR analyses should therefore be interpreted with caution.

		documented in the company's submission documents.	

Issue 3 Conclusion of lack of statistical evidence to support clinical similarity between nivolumab and pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 72/73: "Overall, given the uncertainties in the ITCs, the EAG's view that the results from the FP-NMAs excluding NADIM-II are likely to be the most reliable results for perioperative nivolumab versus perioperative pembrolizumab for EFS and OS, and [redacted], the EAG considers that the company has not provided robust evidence to demonstrate clinical	Across the standard Bayesian NMA, the ML-NMR, and the FP-NMA, point estimates consistently indicate clinical similarity between perioperative nivolumab and pembrolizumab. Point estimates are close to the null value of 1, irrespective of modelling choice; additionally, credible intervals overlap one, suggesting no statistically significant differences.	While the FP-NMA excluding NADIM II is the EAG's preferred analysis, interpretation of the point estimates at later time points should be made cautiously. For EFS, the HR shifts from 0.91 to 1.20 between 3 and 60 months, but credible intervals are extremely wide, especially given that estimates are based on extrapolated data after 48 months. Further, the EFS FP-NMA relies on investigator-assessed outcomes for periPEMBRO+neoCT, whereas periNIVO+neoCT uses BICR-assessed outcomes. The EAG itself has noted that BICR assessments are preferred, as investigator assessments can be biased. Indeed, the BICR assessment for periPEMBRO+neoCT (albeit at an	Not a factual inaccuracy. No change required. As detailed in the EAG report, the company did not report a NIM or MCID for either EFS or OS and therefore the EAG has used a threshold of 0 on the log-axis (which corresponds to a hazard ratio of 1). The setting of the threshold to 0 represents a more conservative estimate compared to if a clinically validated threshold is available. The EAG also acknowledges in the EAG

similarity between nivolumab and pembrolizumab.”		earlier cut-off) yielded a HR closer to the null (0.66 [0.53, 0.83]; database lock: July 29, 2022) compared with the investigator-assessed HRs (0.57 [0.47, 0.69]; August 19, 2024 and 0.58 [0.46, 0.72]; July 29, 2022). It is reasonable to assume that point estimates comparing periNIVO+neoCT vs periPEMBRO+neoCT across timepoints would have been closer to the null had the FP-NMA utilized BICR-assessed EFS for both trials, however, KN671 did not report BICR-assessed EFS for the most recent database lock. Across all models submitted (standard NMA, FP-NMA, and ML-NMR), the results consistently point towards clinical similarity between nivolumab and pembrolizumab. Both agents are PD-1 immune checkpoint inhibitors with the same mechanism of action, providing strong biological rationale for similarity. The point-and-density plots used by the EAG apply a zero-threshold for non-inferiority, which is a conservative standard. While we acknowledge uncertainty	report that when interpreting such probabilities, it has been suggested that a probability of 95% is used to make assessments of non-inferiority. However, the EAG notes that the committee may choose to select an alternative probability threshold.

		remains, particularly for OS, the overall evidence base supports similarity rather than a clinically meaningful difference. The EAG's statement implies that robust evidence of similarity is lacking, which undervalues both the consistency of findings across analytic approaches and the biological plausibility. Clarifying this ensures stakeholders recognize that while statistical uncertainty exists, the weight of evidence points towards clinical similarity. This is critical, as overemphasizing the point estimates from the FP-NMA excluding NADIM II (especially at later timepoints) risks distorting the broader evidence base and may misinform conclusions regarding perioperative nivolumab and pembrolizumab comparability.	

Issue 4 Conclusion of lack of clinical evidence to support clinical similarity between nivolumab and pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14; 30; page 84 "As a general principle, the EAG has concerns with [redacted] is alone sufficient evidence to determine clinical similarity. [redacted]" "Based on the advice of clinical experts, the EAG notes that both perioperative pembrolizumab and	The company proposes the text throughout the document is amended to include the EAG clinical experts' views on the appropriateness of assuming clinical similarity between nivolumab and pembrolizumab.	There is strong opinion from the clinical community that there is no perceived difference between different PD-1 inhibitors, which is not captured in the EAG report. It is not clear if clinical experts were explicitly asked if they consider nivolumab, pembrolizumab or durvalumab to be clinically similar in this setting by the EAG. If this question was asked, the response should be included in the EAG report. The clinical expert view that these treatments are considered similar is missing from the executive summary, the comparators section, and the conclusion, and is an important element of similarity that is omitted. Having consulted with Professor Sanjay Popat (Consultant Medical Oncologist, Head of the Lung	Thank you for highlighting the views of the company's clinical experts on clinical similarity. The following text has been added to the executive summary, the comparators section and Section 8 of the EAG report: The EAG notes that the company's clinical experts expected nivolumab and pembrolizumab to have similar treatment effects, but the EAG considers that ITCs are likely to provide a more robust method to compare the two treatments.

perioperative durvalumab could be considered comparators for perioperative nivolumab.”		Unit, and Lead for the Lung Cancer Research Programme, Royal Marsden Hospital), in his expert opinion “*these agents perform similarly from trial data and there is no strong evidence of pharmacological difference between IV pembro and IV nivo- the two are essentially interchangeable. In terms of clinical practice we do not differentiate and there is no differences between the two drugs”*. A similar clinical view was shared between all other clinical experts from different institutions across England that BMS consulted: *“I do not know of any strong evidence to suggest pharmacological differences between pembro and nivo and as it stands in the early-stage lung cancer arena, I would consider them equally effective*”. Clinician at St Barts Hospital, London “*There is no perceived difference in the community between*	

		different PD1 / PDL1 inhibitors." Clinician at University Hospital Birmingham. "*Checkpoint inhibitors are doing the same thing" and generally considers "PD1/PDL1 inhibitors as interchangeable and equivalent in this clinical setting*". Clinician at Leeds Teaching Hospital.	

Issue 5 Addition of subcutaneous license text

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 82 section 6.3 "Additional feedback from the EAG's clinical experts stated that the differences in administrations in the adjuvant setting would be the greatest barrier to the uptake of nivolumab in clinical practice. Given the practical advantages,	Add: However, the MHRA license for subcutaneous nivolumab administration for nivolumab in this indication was approved on 19th September 2025, specifically for use in the adjuvant phase of perioperative nivolumab administration. The administration time of	Text may be misleading given the new SC MHRA approval for this indication is preferred by clinicians as an administration route compared to IV. As of the 19/09/2025, SC nivolumab was approved for the monotherapy maintenance phase (adjuvant) of perioperative treatment (Q2/Q4W). We appreciate that this approval	Not a factual inaccuracy. No change required.

patients and clinicians are likely to continue to prefer to treat with pembrolizumab, as only seven courses are required, compared to the 13 courses of nivolumab.”	subcutaneous (SC) nivolumab is anticipated to be 3-5 minutes, which may be considered preferable for patients and clinicians in comparison to IV administration, including IV pembrolizumab.	information was unavailable to the EAG when considering the company evidence submission (which was submitted in April 2025), but this approval is of strong relevance to the administration challenges posed by the EAG’s clinical experts. This SC optionality in the adjuvant phase of perioperative treatment is a highly anticipated formulation for clinicians and the NHS. Administering SC nivolumab instead of an IV formulation will alleviate capacity constraints, chair time, clinic time and importantly improve patient experience. **This view has been explicitly expressed by 9 clinical experts across England during insight gathering (please see appendix)**. Administering a SC formulation over 3-5 minutes versus a 30-minute infusion of nivolumab or pembrolizumab is anticipated to significantly reduce chair time. This efficiency has been demonstrated in the real-world	

		setting, with data from Mount Vernon Hospital showing that switching to SC nivolumab from intravenous (IV) across all approved indications resulted in a chair time saving of 105.5 hours between May and August 2025.	

Issue 6 Unclear conclusion in EAG addendum

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21 **“**Overall, given the uncertainties in the ITCs, the EAG’s view that the results from the traditional Bayesian NMAs and FP-NMAs excluding NADIM-II are likely to be the most reliable results for perioperative nivolumab versus perioperative durvalumab for EFS and	**Add**: A concluding remark about what the EAG thinks. Does the evidence point towards nivolumab being favourable? What are you concluding if not clinical similarity?	It is not clear currently what the EAGs view is with regards to the evidence, i.e. why is a conclusion of non-similarity reached? The EAG acknowledge that the point estimates are favourable for nivolumab in all ITC comparisons. The EAG non-inferiority analysis points towards nivolumab being more likely non-inferior than not non-inferior. Why is the EAG not confident in concluding clinical similarity – what more would the EAG need to see to conclude	Not a factual inaccuracy. No change required. Please see the EAG response to Issue 3 for further details on the interpretation of the results from the EAG’s point-and-density plots.

OS, and [redacted], the EAG [redacted] between perioperative nivolumab and perioperative durvalumab.”		clinical similarity? Is the EAG view that nivolumab is favourable, therefore not similar/non-inferior? If so, this should be made clear.	

Appendix: Clinical opinion on the benefits of a subcutaneous (SC) formulation vs IV

- SC would be an incredible change and make a massive difference to their clinic pressures, admin time, and if available they would be keen to make a switch to perioperative nivolumab – clinician from St Barts Hospital, London
- SC would be an absolute “gamechanger” in perioperative lung cancer treatment – clinician from Royal Marsden Hospital, London
- Clinician is very keen on using SC nivolumab in the perioperative setting and the Pharmacy & Procurement would be “ready to go” to implement this when available **–** clinician from Royal Sussex County Hospital
- Hospital is using perioperative pembrolizumab, however if SC nivolumab was available, that would be make a big difference in their provision and even future homecare settings -- clinician from Royal Surrey Hospital
- Keen on a SC approach when available in perioperative Lung -- Guys and St Thomas Hospital
- Prefers a SC formulation over any IV formulation due to capacity issues and the drive to deliver care closer to patients' homes -- Clinician from Freeman Hospital, Newcastle
- A SC formulation would be the preferred option for their site -- clinician from Leeds Teaching Hospital
- SC nivolumab will significantly impact capacity in the perioperative setting – clinician, The Christie, Manchester
- Hospital are using perioperative pembrolizumab, however clinicians are aware of the nivolumab SC license, and SC nivolumab is expected to have a significant impact, being highly attractive. The clinician shared real-world data indicating

that chair time has reduced from 97 minutes to 43 minutes with SC atezolizumab, and it is expected to decrease further with SC nivolumab, which is a 3-5 minute injection- clinician from the Clatterbridge Hospital, Manchester